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THE ROENTGENOLOGIC DISPLACEMENTS IN COLLES' FRACTURE

WITH SPECIAL REFERENCE TO THE MECHANISM OF THE
ACCOMPANYING FRACTURE OF THE ULNAR STYLOID:

A REPORT OF ONE HUNDRED CONSECUTIVE
CASES *

LOUIS CARP, M.D.

NEW YORK

This study was undertaken to show: (1) the usual roentgenologic displacements in Colles' fracture with an accompanying fracture of the styloid process of the ulna and the practical therapeutic value of such information, and (2) the probable mechanism of fracture of the ulnar styloid. According to Schinz,¹ this fracture occurs in 58 per cent of all Colles' fractures.

A study of the table will demonstrate the most frequent positions of the lower radial fragment (Darrach²) in this series of cases, as follows:

	Percentage
Impaction only.....	29
Dorsal tilt with impaction.....	17
Dorsal tilt with dorsal displacement.....	12
Dorsal tilt with dorsal displacement and impaction.....	12
Dorsal tilt.....	9
Simple fracture, no displacement.....	4
Dorsal tilt, dorsal displacement, radial shift.....	4
Ventral tilt with impaction.....	3
Dorsal displacement with impaction.....	3
Dorsal tilt, impaction, radial shift.....	2
Dorsal displacement.....	2
Ventral tilt, ventral displacement, impaction.....	1
Dorsal tilt, dorsal displacement, radial shift.....	1
Dorsal tilt, radial shift.....	1

From these statistics it may be inferred that, generally speaking, Colles' fractures with accompanying ulnar styloid fractures have enough roentgenologic displacements to warrant their reduction. Experience has taught that lack of gross deformity does not necessarily mean a lack

* Submitted for publication, Feb. 24, 1931.

* From the Fracture Clinic of Dr. William Darrach, the Presbyterian Hospital, and the College of Physicians and Surgeons, Columbia University.

1. Schinz, Hans R.: Der Abbruch des Processus styloideus ulnae, Deutsche Ztschr. f. Chir. **125**:81, 1922.

2. Darrach, William: Fractures of the Lower Extremity of the Radius; Diagnosis and Treatment, J. A. M. A. **89**:1683 (Nov. 12) 1927.

Analysis of Roentgenologic Findings in One Hundred Consecutive Cases of Colles' Fracture with Accompanying Fracture of the Ulnar Styloid

[illegible]

of roentgenologic displacement. Since, in Colles' fracture in particular, roentgenologic fragment reduction of the radius is so important in the majority of cases for production of good anatomic and functional end-results, the foregoing statistics indicate the necessity of careful study of the roentgenogram before reduction or immobilization is attempted.

THE MECHANISM OF FRACTURE OF THE ULNAR STYLOID

It is my belief that in the greatest percentage of cases the ulnar styloid is fractured at the base by a sudden pull of the intra-articular fibrocartilage and at the middle and tip by a sudden pull of the ulnar collateral ligament, and that both ligaments may act together to produce the aforementioned fractures. A small percentage of these fractures may be produced by a sudden impact of the carpus against the ulnar styloid.

In order that these theories might be substantiated, the problem was approached from the following angles:

1. An anatomic study was made of the ligamentous attachments to the ulnar styloid to determine lines of stress and strain with respect to the accompanying fracture of the radius and the other bony structures. It was felt that experimental production in the cadaver of the fractures under discussion would be difficult, and that any definite conclusions would be unwarranted (Cotton,³ Gallois⁴).

2. A notation was made of the sites of fracture of the styloid process, with their various displacements, as shown by the roentgenograms (figs. 1, 2 and 3).

3. The positions and displacements of the lower radial fragment, as shown anatomically and roentgenologically, were correlated.

ANATOMIC STUDY OF LIGAMENTS ATTACHED TO THE ULNAR STYLOID

The wrist joints of twenty-two cadavers were dissected in order to note especially the ligamentous attachments to the ulnar styloid (fig. 4). The two chief structures that produce stress and pull on the styloid are the intra-articular triangular fibrocartilage and the ulnar collateral (internal lateral) ligament.

The Triangular Fibrocartilage.—This ligamentous attachment is triangular, its base being joined to the mesial portion of the articular surface of the lower end of the radius and its apex to the notch at the

3. Cotton, F. W.: *Experimental Colles's Fracture*, Boston Soc. M. Sc. 2:171, 1897-1898.

4. Gallois, E.: *Fracture de l'extrémité inférieure du radius; étude radiographique, physiologique et expérimentale*, Lyon, L. Bourgeon, 1898.



Fig. 1.—Types of fractures of the ulnar styloid accompanying Colles' fracture probably produced by pull of the intra-articular fibrocartilage: *A*, dorsal tilt, dorsal displacement, impaction; fracture of the middle of the ulnar styloid with lateral shift of 0.5 cm. and angulation of 90 degrees. *B*, dorsal tilt, dorsal displacement, impaction; fracture of the base of the ulnar styloid, with lateral shift of 1 cm. and angulation of 10 degrees. *C*, dorsal tilt, dorsal displacement, impaction, dorsal free fragment; fracture of the middle of the ulnar styloid with slight lateral shift. *D*, dorsal tilt, dorsal displacement, radial shift; fracture of the base of the ulnar styloid without displacement. *E*, dorsal tilt, dorsal displacement, impaction, radial shift; fracture of the base of the ulnar styloid with angulation of 45 degrees.

base of the ulnar styloid. It articulates both bones firmly. Its anterior and posterior borders are united with the anterior and posterior radio-ulnar ligaments. Both surfaces are covered by synovial membrane. The following additional observations were noted:

1. The triangular fibrocartilage is about 1.1 cm. long at its base and the same length from apex to base.

2. It is very strong at its periphery and becomes thinner at its center and at the lesser sigmoid cavity of the radius. In three specimens, the thin central portion was found to be completely eroded. It is difficult to say whether this occurred ante mortem or post mortem.

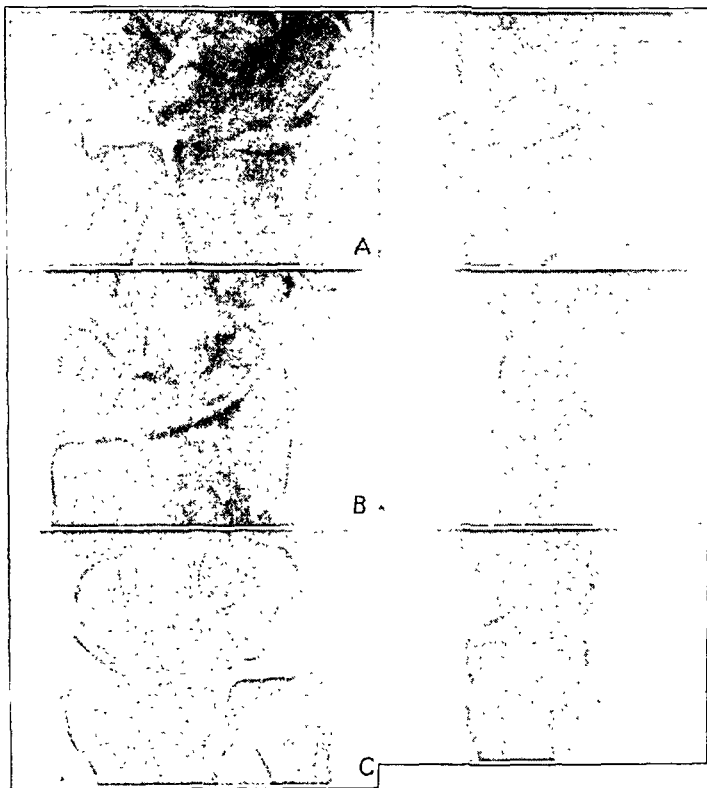


Fig. 2.—Types of fracture of the ulnar styloid accompanying Colles's fracture, probably produced by pull of the ulnar collateral ligament: *A*, ventral tilt with impaction; fracture of the tip of the ulnar styloid with lateral shift of 0.2 cm. and lateral angulation of 45 degrees. *B*, impaction; fracture of the tip of the ulnar styloid without shift or angulation. *C*, dorsal tilt, impaction; fracture of the tip of the ulnar styloid without shift or angulation.

3. The reinforcements of the anterior and posterior radio-ulnar ligaments are important structures.

4. The central fibers form a thick, strong strand of fibrous tissue which attaches itself intimately in an arched direction to the notch at the base of the ulnar styloid. Up to this point the fibrocartilage does not attach itself to the ulna.

5. In sixteen of the twenty-two specimens, additional weaker fibers of the fibrocartilage attached themselves along the entire radial border of the ulnar styloid.

6. In five specimens, additional weaker fibers of the fibrocartilage attached themselves along only a part of the radial border of the ulnar styloid.

7. In one specimen, the fibrocartilage inserted only in the notch at the base of the ulnar styloid.

8. There is a small blood vessel that enters the arched fibers of the fibrocartilage. It seems to come from the bone.

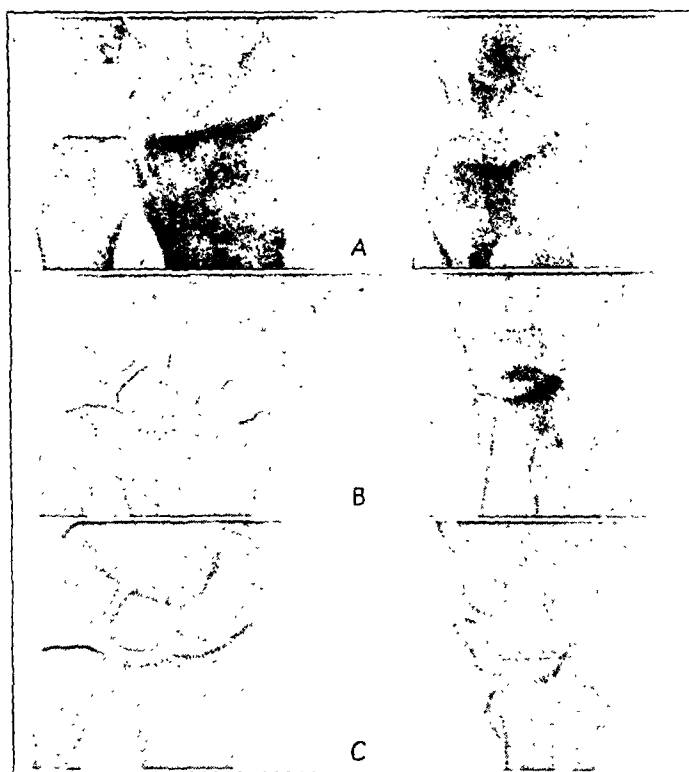


Fig. 3.—Types of fractures of the ulnar styloid accompanying Colles' fracture, probably produced by a combined pull of the intra-articular fibrocartilage and ulnar collateral ligament: *A*, dorsal tilt, impaction and radial shift; fractures of the base and middle of the ulnar styloid with lateral shifts of the fragments of 0.1 and 0.2 cm., respectively, and angulation of 20 degrees. *B*, dorsal tilt, dorsal displacement, impaction; fractures of the base and tip of the ulnar styloid, with lateral shift of 0.5 cm. *C*, dorsal tilt impaction; fractures of the base, middle and tip of the ulnar styloid.

The function of the triangular fibrocartilage is to cushion the carpus against the radio-ulnar joint and to limit pronation and supination at the wrist joint.

The Ulnar Collateral (Internal Lateral) Ligament.—This is a strong, fan-shaped, cordlike structure the apex of which is attached to

the ulnar styloid. From the apex it spreads out and divides into an anterior and posterior fasciculus; the former, passing down vertically, is attached to the inner side of the cuneiform bone, the latter to the base of the pisiform bone and annular ligament. The following additional notations were made from the dissections:

1. The tendon of the extensor carpi ulnaris, by grooving the ulnar collateral ligament on its dorsal surface, throws up the fibers mesially in a thick, cordlike structure which passes mostly to the tip of the styloid process.

2. The anterior fasciculus spreads out along the radial border of the ulnar styloid and from there continues up to the ulnar head.

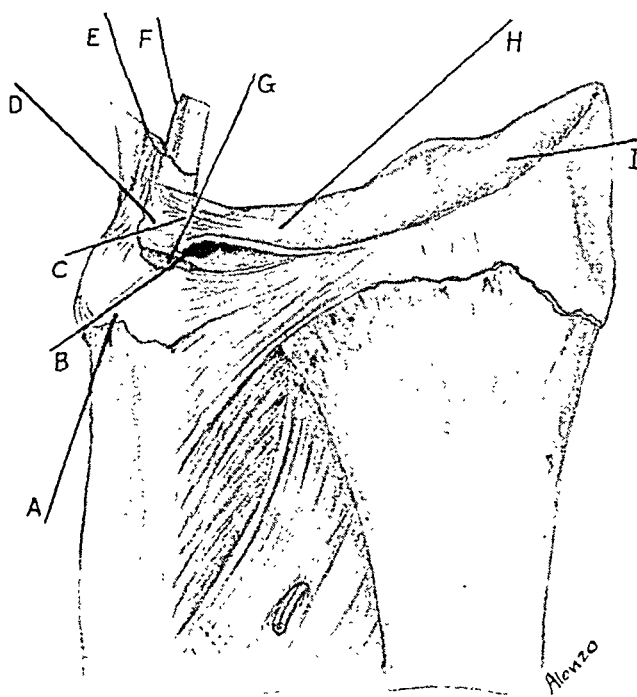


Fig. 4.—Drawing from a dissection to show the anatomy of the intra-articular triangular fibrocartilage and the ulnar collateral ligament. *A* indicates the anterior fibers of the ulnar collateral ligament; *B*, the thickened arcuate fibers of the triangular fibrocartilage inserting into the notch at base of ulnar styloid; *C*, additional fibers of the triangular fibrocartilage inserting into the radial surface of the ulnar styloid; *D*, the styloid process of the ulna; *E*, the posterior fibers of the ulnar collateral ligament thrown into a strong fold by a tendon of the extensor carpi ulnaris; *F*, the tendon of the extensor carpi ulnaris; *G*, the ulnar articular surface; *H*, the triangular fibrocartilage (note the thin central portion) and *I*, the articular surface of the radius.

3. The fibers of the anterior fasciculus nearer the joint surface have a tendency to insert on the radial aspect of the ulnar styloid if the triangular fibrocartilage is not attached all along its length.

The action of the ulnar collateral ligament is to limit pronation, supination, extension and abduction of the wrist.

ROENTGENOLOGIC FINDINGS

The following is a summary of the analysis presented in the table:

1. Almost half of the fractures of the ulnar styloid accompanying Colles' fracture occur at its base.
2. In all the fractures of the ulnar styloid, including the base, middle and tip, 29 per cent occurred with impaction only of the radius fracture.
3. When the alinement between the lower radial fragment and the shaft of the radius was disturbed, there was in the greatest percentage of cases lateral shift, lateral angulation or both in the fractured ulnar styloid.

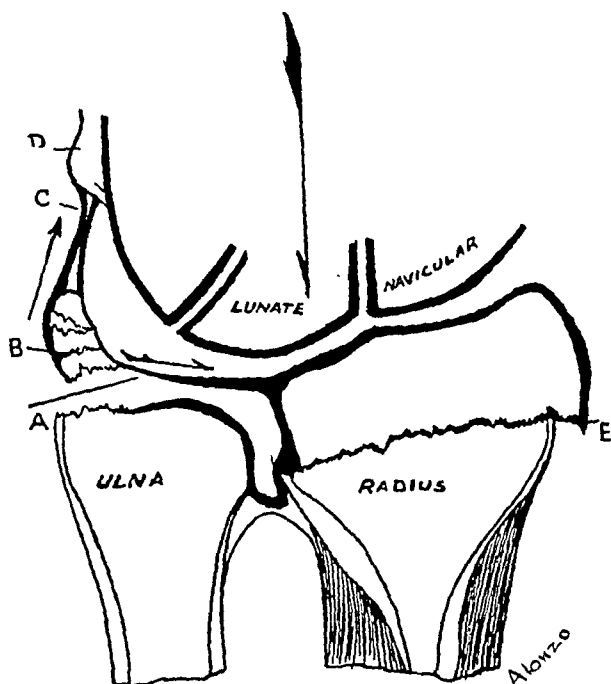


Fig. 5.—Diagrammatic view of a vertical section of the wrist showing the probable mechanism of fracture of the base of the ulnar styloid by the intra-articular fibrocartilage and of the middle and tip of the ulnar styloid by the ulnar collateral ligament (arrows show direction forces). *A* indicates the triangular fibrocartilage; *B*, the ulnar styloid; *C*, the ulnar collateral ligament; *D*, the pisiform bone, and *E*, the line of fracture.

4. With impaction only of the radius accompanied by fracture of the middle of the ulnar styloid, there was lateral shift of the styloid fragment in two thirds of the cases; accompanied by fracture of the tip, there was lateral shift in two fifths of the cases; accompanied by fracture of the base, there was no instance of shift.

5. Lateral shift of the ulnar styloid is more than twice as frequent as lateral angulation.

6. Medial shift and medial angulation of the ulnar styloid are rare.

7. Fracture of the ulnar styloid accompanying simple fracture (no displacement or impaction) of the lower end of the radius is relatively infrequent. There were only four cases in the series.

CORRELATION OF THE ANATOMIC AND ROENTGENOLOGIC FINDINGS

Mechanism of Fracture of the Base of the Ulnar Styloid (fig. 5).—The relation of the intra-articular fibrocartilage to the ulnar styloid and the pull it exerts from the radial fragment make it logical to assume that in the greatest percentage of cases the pull on the ulnar styloid by the fibrocartilage produces a fracture at its base. This pull is produced by a forceful impact of the carpus against the fibrocartilage and by a sudden strain on the fibrocartilage by the displaced lower radial fragment. Part of the ligamentous pull may be spent by a tear in the ligament.

Roentgenologic Findings in Support of Foregoing Theory.—Impaction plus tilts plus displacements of the radial fragment (or their combinations) produced forty-one fractures of the base of the ulnar styloid. In these forty-one fractures there were twenty-one lateral and three medial shifts, ten lateral and one medial angulations.

The great preponderance of lateral shifts and angulations of the styloid process seems to indicate a pull by the fibrocartilage from its point of origin on the radius.

Mechanism of Fracture of the Middle of the Ulnar Styloid (fig. 5).—The mode of attachment of the ulnar collateral ligament seems to make it the logical factor for the production of fracture of the ulnar styloid at this site in the greatest percentage of cases. The dissociation of the anatomic relations at the wrist joint, especially with a medial shift of the carpus, tends to put undue tension on the ulnar collateral ligament. Part of the ligamentous pull may be spent by a tear in the ulnar styloid, or both.

Roentgenologic Findings in Support of Foregoing Theory.—Impactions plus tilts plus displacements of the radial fragment (or their combinations) produced twenty-eight fractures of the middle of the ulnar styloid. In these twenty-eight fractures there were eighteen lateral shifts and seven lateral and one medial angulations.

Mechanism of Fracture of the Tip of the Ulnar Styloid (fig. 5).—It is logical to assume that the ulnar collateral ligament is responsible for the largest percentage of fractures of the tip of the ulnar styloid because of the way it is attached to this bone.

Roentgenologic Findings in Support of Foregoing Theory.—Impactions plus tilts plus displacements of the radial fragment (or their com-

bbinations) produced twenty-three fractures of the tip of the ulnar styloid. In these twenty-three fractures there were thirteen lateral shifts and four lateral angulations.

Mechanism of Fracture of the Base and Middle or Base and Tip of the Ulnar Styloid.—This type of fracture is probably produced by a combined action of the fibrocartilage and ulnar collateral ligament.

Roentgenologic Findings in Support of Foregoing Theory.—Impactions plus tilts plus displacements of the radial fragment (or their combinations) produced two fractures of the base and middle of the ulnar styloid. In these two fractures there were one lateral shift and one lateral angulation.

Impactions plus tilts plus displacements of the radial fragment (or their combinations) produced two fractures of the base and tip of the ulnar styloid. In these two fractures there were two lateral shifts and one lateral angulation.

Fracture of the ulnar styloid by direct violence is necessarily rare because it is such a small bony process, very well protected by soft structures. It is likely that fractures that have a medial shift or angulation may be broken by direct forceful impact of the carpus against the styloid process.

SUMMARY

1. Most Colles' fractures accompanied by fractures of the ulnar styloid have sufficient (96 per cent) displacements of the lower radial fragment to warrant reduction in order to obtain the best possible anatomic realinement which is usually essential for the best end-results.

2. A correlation of roentgenologic and anatomic findings suggests that the ulnar styloid in Colles' fracture, in the great majority of cases, is fractured at the base by the pull of the intra-articular fibrocartilage of the wrist joint and at the middle and tip by the pull of the ulnar collateral ligament. It is logical to assume that both ligamentous structures may act together to produce fracture of the ulnar styloid, especially when the fracture occurs in two or three places simultaneously. Direct violence probably plays a negligible rôle in any of the fractures of the ulnar styloid, although forceful sudden impact of the carpus against the styloid may be the cause in a very small percentage of the cases.

QUOTATIONS FROM THE LITERATURE ON MECHANISM OF FRACTURE OF THE ULNAR STYLOID IN COLLES' FRACTURE

I believe that there are two factors at work: the internal lateral ligament which tears off the tip and the triangular fibrocartilage which produces fracture near the base. (Fullerton⁵)

5. Fullerton, A.: Colles' Fracture, M. Press 79:555, 1905.

The fragment of the ulnar styloid is usually so small that it is torn away by a twist of the internal lateral ligament at its point of insertion. (Hennequin⁶)

With the displacement of the radius either the ligaments must rupture or the ulnar styloid must be broken. (Duplay⁷)

If the hand is in adduction the semilunar bone receives the whole weight and the triquetral becomes approximated to the ulna, the styloid process of which may be torn by pressure on the fibrocartilage. In hyperextension the styloid may be torn either by pressure of the semilunar on the triangular fibrocartilage or by traction of the internal lateral ligament. (Gallois⁴)

When the radius breaks and the fracture forces continue to act, the hand is forcibly turned inwards and upwards, thus putting the cord-like internal lateral ligament on the stretch and in a test of strength between the ligament and the bone, the latter gives way. (Van Lennep⁸)

The displacement of the radius may produce fracture of the ulnar styloid (65%), rupture of the fibrocartilage or internal lateral ligament or combinations of these. If the cartilage holds, the styloid will yield, and if it does the continued pull may suffice to tear the internal lateral ligament. (Swett⁹)

Sometimes the styloid process is broken off, apparently by avulsion through the lateral ligament or possibly the fibrocartilage. (Stimson¹⁰)

Fracture of the ulnar styloid is probably due to traction of the lateral ligament, pull of the triangular fibrocartilage, or direct violence. (Cotton³)

The internal lateral ligament attached to the ulnar styloid may be torn off or its angle of pull changed or it may wrench off the end of the styloid process maintaining its own fibres intact. (Speed¹¹)

The styloid process, intimately attached to the fibrocartilage is fractured by a push of the carpus against the fibrocartilage. (Destot.¹²)

The ulnar styloid may be fractured by the internal lateral ligament or the triangular fibrocartilage. In the experimental work of Gallois, the weaker ulnar styloid was found attached to the fibrocartilage. (Schinz¹)

The fracture may be due to either ligament but a complete radial shift of the radial fragment is very unusual so that the internal lateral ligament is probably the causative factor. (Poulsen.¹³)

6. Hennequin, J., and Loewy, R.: *Fractures des os*, Paris, Masson et Cie, 1904.

7. Duplay, S. E.; Rochard, J. E., and Demoulin, A.: *Diagnostic chirurgical*, Paris, O. Doin, 1921.

8. Van Lennep, G. A.: Is the Break in the Radius the Only Bone Lesion in Colles's Fracture? *Hahneman. Monthly* **34**:621, 1899.

9. Swett, P. P.: *Colles' Fracture with Special Reference to the Lateral Deformity*, New York M. J. **90**:148, 1909.

10. Stimson, L. A.: *A Practical Treatise on Fractures and Dislocations*, Philadelphia, Lea & Febiger, 1917.

11. Speed, K.: *A Text-book of Fractures and Dislocations*, Philadelphia, Lea & Febiger, 1928.

12. Destot, Etienne: *Traumatismes du poignet et rayons X*, Paris, Masson et Cie, 1923.

13. Poulsen, K.: Studien ueber die sogenannte typische Fractur des Radius, *Arch. f. klin. Chir.* **80**:902, 1906.

It is difficult to tell which ligament produces the fracture, because the ligamentous attachments may vary from the base of the styloid to the tip. (Essau¹⁴)

Direct trauma is hardly likely. Delbet proved that the internal lateral ligament was strong enough to tear off the styloid process. The internal lateral ligament is the most important factor in the fracture. Rochard and Demoulin believe the fibrocartilage to be the causative agent, but the author objects because it would not explain a fracture of the tip. Further if the fibrocartilage inserts at the base of the styloid it would not produce any lesion except a longitudinal line of fracture following the bony canals. This does not occur. (Bouygues.¹⁵)

14. Essau, P.: Ueber die isolierte Fractur des Processus styloides ulnae, Arch. f. Orthop., Wiesb. **11**:42, 1911.

15. Bouygues, J.: Des fractures isolés de l'extrémité inférieure du cubitus, Faculté de Médecine de Paris, Thèse, no. 378, 1904, p. 1.

THE PATHOGENESIS OF THE "STRAWBERRY" GALLBLADDER

(CHOLESTEROSIS OF THE GALLBLADDER) *

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AND

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ST. LOUIS

Moynihan,¹ in 1909, first called attention to small yellowish spots like sand or grit on the mucosa of the gallbladder. In such cases he noticed also that the bile sometimes shimmered because of the presence of cholesterol crystals. In the following year, MacCarty,² because of the appearance of the organ in these cases, used the descriptive term of "strawberry" gallbladder. Lichtwitz,³ in 1914, pictured a beautiful instance of the condition and stated that according to his surgical colleagues it was a not infrequent finding at operation. He was not aware that Moynihan and MacCarty had already described it before him. For a time its existence was generally overlooked, and it is true that such a gallbladder may, from its external appearance, seem quite normal and occasionally on microscopic section may show a minimum of inflammatory change. The gross appearance of the mucosa is striking, however, and in recent years it has become more generally known and is now claimed to comprise about one fifth of all types of diseased gallbladders removed at operation.⁴

Boyd⁵ published the first detailed study of the pathology of this remarkable condition. He demonstrated the lipid nature of the white or yellow deposits that are seen with the naked eye in striking contrast to the dark red background of the rest of the mucosa. By histologic and chemical means he also showed that these lipid-like deposits were cholesterol, an observation, however, that Lichtwitz³ was really the first to make. The most recent study of Illingworth⁴ added much to the knowledge of this type of gallbladder disease, clinically as well as experimentally.

* Submitted for publication, July 30, 1931.

* From the Department of Surgery, Washington University School of Medicine, and Barnes Hospital.

1. Moynihan, B. G. A.: A Disease of the Gallbladder Requiring Cholecystectomy, *Ann. Surg.* **50**:1265, 1909.

2. MacCarty, W. C.: *Ann. Surg.* **51**:651, 1910.

3. Lichtwitz, L.: *Ergebn. d. inn. Med. u. Kinderh.* **13**:1, 1914.

4. Illingworth, C. F. W.: *Brit. J. Surg.* **17**:203, 1929.

5. Boyd, W.: *Brit. J. Surg.* **10**:337, 1922.

The explanation of these extensive cholesterol deposits has generally been that there was a disturbance in the normal absorbing power of the gallbladder mucosa for this substance. Aschoff⁶ was apparently the first to maintain that cholesterol is normally taken up by the wall of the gallbladder from the bile. Boyd⁵ adopted this theory, adding a bit of indirect evidence of his own in its support. Illingworth⁴ also accepted it, though with some reserve, on the basis of additional experiments. Mentzer,⁷ arguing inferentially from his own observations, also believed that cholesterol was absorbed by the gallbladder. This theory seems to have been generally adopted by most surgeons at the present time.

In contrast to these views, evidence has been obtained in a series of experiments in this laboratory that seems to show that: (1) the gallbladder does not absorb cholesterol; (2) it has the power of excreting cholesterol, and (3) inflammation may accelerate this excretion. Its bearing on the problem of the pathogenesis of the "strawberry" gallbladder is obvious.

Some of this evidence in favor of the excretion of cholesterol has been briefly described in preliminary communications from this laboratory,⁸ but will be presented in detail later in this article. Additional data will be found together with a complete discussion of the cholesterol function of the gallbladder in another report.⁹ Our experimental and clinical evidence may be conveniently summarized as follows:

1. When the gallbladder was isolated by ligature of the cystic duct, the bile therein after a sojourn of from two to sixteen days came to contain a larger amount of cholesterol in all but one of nine experiments (tables 1 and 2). In these eight dogs the gallbladder contents (after corrections due to change in volume through dilution or concentration) showed increases of 520, 54, 88, 77, 18, 49, 400 and 151 per cent in their total cholesterol over that present at the time the cystic duct was tied. In one dog there was a decrease of 14 per cent, an amount that we believe was perhaps within the experimental error. These increases obviously could have come only from the wall of the gallbladder. Torinomi,¹⁰ whose results have been repeatedly quoted in proof of the absorption theory, had performed several experiments similar to these. In three dogs he found definite decreases in the total cholesterol, but they were not marked. In two dogs he found an increase, as we did, but he stated that the tissue showed inflammatory

6. Aschoff, L.: München. med. Wchnschr. **38**:1847, 1906.

7. Mentzer, S. H.: Am. J. Path. **1**:383, 1925.

8. Elman, R., and Taussig, J. B.: Proc. Soc. Exper. Med. & Biol. **28**:1066, 1931.

9. Elman, R., and Taussig, J. B.: J. Exper. Med. **54**:775, 1931.

10. Torinomi, K.: Beitr. z. path. Anat. u. z. allg. Path. **72**:456, 1924.

TABLE 1.—*Increases in Cholesterol Concentration of Bile After a Sojourn in the Gallbladder (by Ligature of the Cystic Duct) **

Dog	Duration of Experiment, Days	Cholesterol of Bile			Concentration of Bile as Shown by Bilirubin Content			Condition of Gallbladder at Autopsy
		At Operation, Mg./Cc.	At Autopsy, Mg./Cc.	Change in Percentage	At Operation, Mg./Cc.	At Autopsy, Mg./Cc.	Change in Percentage	
25	6	0.42	2.71	+520	0.071	0.071	0	Gallbladder full of thick mucoid bile; no signs of infection in the gross
A	1	0.50	0.88	+ 76	0.041	0.050	+ 22	Gallbladder full of thick bile
B	2	0.75	1.45	+ 93	0.061	0.127	+107	Gallbladder full of thick bile
320	14	0.95	1.20	+ 26	0.92	0.34	— 62	Gallbladder full of thin mucoid bile; section shows no inflammatory changes
324	13	1.15	1.50	+ 31	1.3	0.70	— 46	Gallbladder full of thin mucoid bile; section shows dilated vessels but no leukocytic infiltration
166	15	0.79	1.4	Gallbladder shrunken and contained colorless debris, which consisted of cholesterol crystals; section showed a thick wall but no inflammation or fibrosis
WH	7	0.42	0.78	+ 86	3.33	1.18	— 65	Gallbladder contained thick mucoid bile; section showed moderate inflammatory changes; mucosa contained much cholesterol

* That this increase was not due to concentration of the bile is shown by the figures on bilirubin, which in three cases show that the bile was actually diluted during its sojourn.

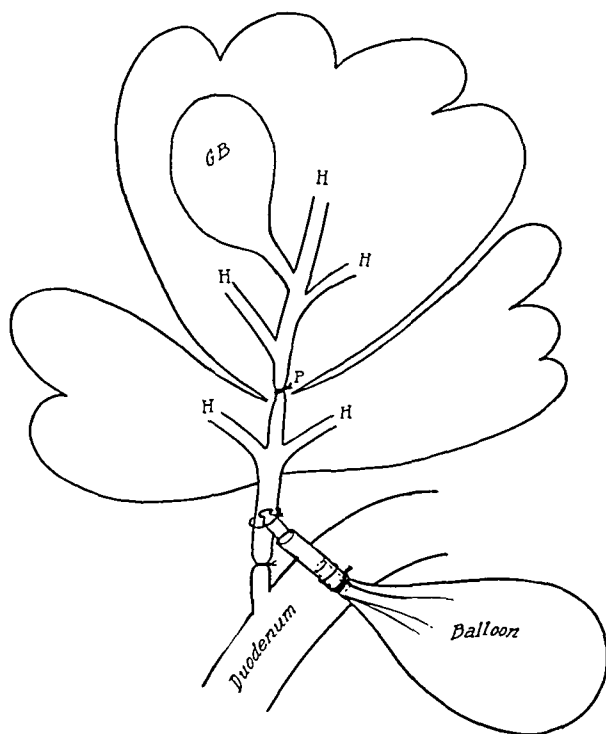
TABLE 2.—*Increase in Total Cholesterol of Bile During its Isolation in the Gallbladder by Ligation of a Cystic Duct **

Dog	Duration of Experiment, Days	At Operation			At Autopsy			Increase in per Cent	Condition of Gallbladder
		Cholesterol, Mg./Cc.	Amount of Bile, Cc.	Total Cholesterol, Mg.	Cholesterol, Mg./Cc.	Amount of Bile, Cc.	Total Cholesterol, Mg.		
B45	16	0.36	10	3.6	1.94	8.0	15.52	300	Mucosa showed much cholesterol in section; no signs of inflammatory change
WH	3	0.27	15	4.1	0.76	8.0	6.10	49	Mucosa showed some edema of stroma but no infiltration of leukocytes
S80	2	0.50	13	6.5	0.90	8.5	7.65	18	Section showed only edema of wall; localized peritonitis; peritoneal fluid contained 1 mg. per cc. of cholesterol

* The total content was removed and a measured amount reintroduced, leaving only enough for analysis.

changes on section. Infection was present in only a few of our experiments, but we believe that the increase was more marked in them.

2. Experiments designed to compare bile subjected to gallbladder influence with that flowing directly from the liver, in the same dog, showed a much greater concentration of cholesterol in the former even when one corrected for the inspissating effect of the gallbladder.⁸ The accompanying sketch shows diagrammatically the nature of these experiments. In one dog the bile in connection with the gallbladder contained 1.1 mg. of cholesterol per cubic centimeter, whereas that coming directly from the liver contained but 0.06 mg. In five other experiments,



Diagrammatic sketch of one series of experiments summarized in the text (see table 3). The partitioning ligature (*P*) separated the bile in two parts. (The gallbladder was first emptied.) The upper part of the liver drained into the gallbladder (*GB*); the lower part directly into the balloon. *H* indicates the hepatic ducts.

although the bile pigment output by the two parts of the liver drained was equal, the cholesterol output by the part still connected with the gallbladder was 0.38, 0.20, 0.059, 0.077 and 0.105 mg. per gram of liver, whereas the cholesterol output by the rest of the liver was 0.15, 0.09, 0.047, 0.065 and 0.063 mg. per gram of liver, respectively. In other words, the bile made to come in contact with the gallbladder contained thereby 153, 122, 27, 18 and 67 per cent more cholesterol than that which had not. Table 3 summarizes the findings in detail.

TABLE 3.—*Increase in Bile Cholesterol from Contact with the Gallbladder**

Dog	Duration of Experiment, Hours	Gallbladder Bile					Hepatic Bile					Comment †	
		Liver Drained, Gm.	Choles-terol, Mg. per Cc.	Bili-rubin, Mg. per Cc.	Amount, Cc.	Bili-rubin, Mg. per Gm. of Liver	Choles-terol, Mg. per Gm. of Liver	Bili-rubin, Mg. per Gm.	Liver Drained, Gm.	Choles-terol, Mg. per Cc.	Bili-rubin, Mg. per Cc.		Amount, Cc.
Y	48	265	0.72	8.58	14	0.45	0.38	0.49	172	0.13	4.25	20	Gallbladder section showed acute inflammatory changes; regular diet
P	48	300	0.73	2.86	75	0.72	0.20	0.71	115	0.074	0.77	140	Gallbladder grossly normal; high cholesterol diet (eggs)
AA	48	51	1.2	12.00	2.5	0.59	0.059	0.62	192	0.15	2.00	60	Liver pale at operation and autopsy; high cholesterol diet (brains); gallbladder small and shrunken
BB	48	135	0.74	6.67	14	0.69	0.077	0.49	65	0.19	1.43	22	High cholesterol diet (brains); gallbladder looked normal, and showed no inflammatory changes on section
EE	49	100	0.75	10.5	14	1.61	0.105	1.47	332	0.097	2.50	215	Gallbladder looked normal and showed no inflammatory changes on section; regular diet

* Comparative cholesterol and bilirubin concentrations of hepatic and gallbladder bile were obtained simultaneously from the same dogs. A partitioning ligature was placed so that part of the bile was diverted to the gallbladder and part was collected in a balloon (see legend of figure). The middle columns show the output of cholesterol per gram of liver drained. The bile from the gallbladder in each case contained much more cholesterol than the other sample.

† Bile was removed from gallbladder at operation by puncture through liver in all cases except dog EE, in which catheter was used and passed up the common duct.

3. Analyses of "white" bile, a product obtained from the isolated bile ducts, showed the presence of cholesterol, which suggests that the entire biliary tract is able to secrete this substance. The colorless contents in human cases of hydrops of the gallbladder also contained cholesterol, a finding that indicates that it had not only not been absorbed with the other biliary constituents but had probably been secreted by the wall of the viscus. Table 4 shows the details of these observations.

TABLE 4.—*Cholesterol Content of the Fluid in Hydrops of the Gallbladder and of the So-Called "White Bile"*

Case	Cholesterol Content, Mg. per Cc.	Description
G. C. C.	0.45	Hydrops of gallbladder removed at operation; many small cholesterol stones in gallbladder and one large one impacted in cystic duct; section of wall showed no inflammation
J. J. E.	0.19	Hydrops of gallbladder removed at operation; wall thick and inflamed; mucous membrane contained cholesterol on section; tiny cholesterol stones adherent to its surface
R. M.	Macroscopic cholesterol crystals	Chronically inflamed gallbladder removed at operation, containing colorless bile
S. J.	Macroscopic cholesterol crystals	Carcinoma obstructing cystic duct; gallbladder full of colorless debris containing cholesterol crystals
Dog Q.....	0.047	Common duct isolated between ligatures and intubated; 3 cc. collected in rubber balloon during forty-eight hours; sediment contained cholesterol crystals but no bacteria
Dog T.....	0.085	Same experiment; 4 cc. of clear secretion collected in forty-eight hours; no evidence of infection
Dog HH.....	0.074	Same experiment; 9.9 cc. of colorless secretion in seventy-two hours; section of common duct showed no inflammation
Dog GG.....	0.047	Same experiment; 10 cc. collected in ninety-six hours; section showed slight inflammatory changes
Dog S30.....	0.20	Same experiment; 2 cc. of secretion in forty-eight hours; heavily infected; section showed acute inflammatory signs
Dog 13.....	0.22	Accidental total biliary obstruction; 5 cc. of infected colorless secretion from dilated hepatic ducts
Dog B44.....	0.50	Cystic duct tied and gallbladder intubated six days before; 2 cc. of infected secretion collected

4. Comparative analyses⁹ of gallbladder and hepatic bile from the same source (human as well as canine) showed that the cholesterol content of the former is much greater than can be accounted for by concentration of the bile. In a series of four dogs, the gallbladders were removed at operation and the common duct drained. The cholesterol concentration of the gallbladder bile was 230, 370, 511 and 490 per cent greater than the average of the hepatic bile collected subsequently in each case. That these figures were not due to inspissation of the bile by the gallbladder was shown by the comparative bilirubin

concentrations;¹¹ i. e., in the four dogs, respectively, there were — 27, + 2, + 77 and — 46 per cent differences in the gallbladder over the hepatic bile. In other words, the bile was concentrated to the extent of but 2 and 77 per cent in two of the dogs, whereas in the other two there was actually a dilution in the gallbladder (presumably due to the secretion of mucus). These specimens were all sterile. In a series of six human beings on whom cholecystectomy was performed similar changes were observed. In three of them the gallbladder bile and hepatic bile were obtained simultaneously, the latter through aspiration of the common duct at operation. In the other three the common duct was drained, and hepatic bile was obtained subsequent to operation. All specimens were filtered to exclude cholesterol-containing cells or débris. The differences in cholesterol content of the gallbladder over the hepatic biles in five of them were + 350, + 470, + 720, + 71 and + 105 per cent, whereas the differences in bilirubin content were + 74, + 44, + 226, + 11 and + 33 per cent, respectively. In other words, the cholesterol content of the gallbladder bile was greater than could be accounted for by concentration of the bile alone. The obvious inference is that the gallbladder mucosa had contributed to this increase.

COMMENT

To explain the development of the "strawberry" gallbladder on the basis of absorption of cholesterol seems unwarranted from the evidence mentioned. It is difficult to see, moreover, how one can explain the storage of cholesterol according to this theory. This substance is found in great quantities in the stroma of the mucosa, and if it had arrived there by absorption through the epithelial cells, what had prevented it from going further? It has been suggested that inflammation may have obstructed the lymphatics, its normal path of absorption. However, proof of this idea is still lacking. Winkenwerder¹² has shown experimentally, for example, that for certain soluble substances the blood vessels and not the lymphatics are the most important pathway of absorption from the gallbladder. Moreover, obstructed lymphatics have not been demonstrated in the "strawberry" gallbladder. Attempts, finally, in this laboratory to produce cholesterosis of the gallbladder by obstructing lymphatics have uniformly been unsuccessful.¹³

In contrast to the inadequacies of this theory, the "strawberry" gallbladder is relatively easy to explain on the basis that cholesterol is

11. Since in these experiments bilirubin is indifferent to secretion or absorption by the biliary mucosa, its measurement furnishes a convenient gage of changes in volume due to the action of the gallbladder on the bile.

12. Winkenwerder, W. L.: *Bull. Johns Hopkins Hosp.* 46:272, 1930.

13. Copher, G. H.; Illingworth, C. F. W., and Elman, R.: Unpublished observations.

excreted by its mucosa, particularly in the presence of inflammation. First of all, sufficient evidence has been adduced, it is believed, to indicate that this is a normal phenomenon. The rôle of inflammation in accelerating this excretion is suggested not only by our own experiments, but by the old observation that inflammatory exudates are generally rich in cholesterol.¹⁴ This is of importance, because inflammation of the wall of the "strawberry" gallbladder is usually demonstrable. More cholesterol, moreover, is actually present in the bile in these cases. Illingworth⁴ was apparently the first to make this interesting observation, and in a number of our own analyses we also have found very high values, in one instance as much as 9 mg. per cubic centimeter, or over three times the amount usually present in the bile of other gallbladders not showing cholesterosis. The observation of shimmering cholesterol crystals in the bile of these cases by Moynihan has already been referred to.

The storage of cholesterol under the mucosa thus becomes easily explainable whenever the bile for one reason or another becomes unable to take up any more of it. Bile salts play an important rôle in the solution of cholesterol, and it is of interest to note that these two constituents of the bile behave toward the gallbladder in opposite ways. Rosenthal and Licht¹⁵ have recently shown that bile salts are normally absorbed by the gallbladder wall, and that inflammation accelerates this absorption. If this is confirmed, there is, then, an additional factor that operates in the same direction. Thus, it is theoretically possible for stasis alone, by diminishing the bile salt concentration, to lower the solubility of bile for cholesterol, which may then remain in the wall of the gallbladder because the bile can take up no more of it. Infection makes this mechanism more pronounced and is probably necessary to bring about the marked changes found clinically. This is borne out by the experiments of Illingworth,⁴ who has reproduced the "strawberry" gallbladder in rabbits on a diet high in fat by infecting the wall of this viscus with streptococci obtained from diseased human gallbladders.

On the other hand, one cannot conclude definitely from these theoretical considerations that stasis is a factor of primary importance in the production of the "strawberry" gallbladder because of other clinical evidence that it is difficult to reconcile with such considerations. This evidence is of two kinds. In the first place, it has been shown by Sherwood Moore¹⁶ that the type of person who is least prone to cholelithiasis in general (and this includes both calculi and the "straw-

14. Wells, H. G.: *Chemical Pathology*, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 300.

15. Rosenthal, F., and Licht, H.: *Klin. Wchnschr.* **7**:1952, 1928.

16. Moore, Sherwood: *Am. J. Roentgenol.* **13**:515, 1925.

berry" gallbladder), namely, the asthenic or the splachnoptotic type, shows on cholecystographic examination to have the slowest emptying time of the gallbladder and therefore the most stasis. The type, on the contrary, that is most prone to have cholecystic disease, namely, the asthenic or hypersthenic person, who is robust, with large muscles, and inclined to obesity, normally shows the fastest emptying time of the gallbladder and therefore has the least stasis. In the second place, it is well known, following the observations of Courvoisier, that in the majority of instances of even prolonged obstruction of the common duct by malignant disease, in which there is complete stasis of the bile in the gallbladder, there is a noteworthy absence of gallstones or of cholecystic disease. From all of this the conclusion seems inevitable that infection is the factor of major importance in the pathogenesis of the "strawberry" gallbladder.

SUMMARY

Experiments have been described and the evidence discussed to show that the gallbladder excretes (rather than absorbs) cholesterol, particularly in the presence of inflammation. An explanation of the pathogenesis of the "strawberry" gallbladder is presented on this basis.

NOTE.—Since this article was submitted for publication the papers of Andrews, Schoenheimer and Hrdina¹⁷ have appeared. These authors also have found that after ligation of the cystic duct there is an increase in the amount of cholesterol in the gallbladder, but they expressed the belief that the increase is due to a differential absorption of bile acids and cholesterol. They apparently did not take into consideration the possibility of the excretion of cholesterol by the mucosa of the organ.

17. Andrews, E.; Schoenheimer, R., and Hrdina, L.: Etiology of Gall Stones: I, II and III, *Proc. Soc. Exper. Biol. & Med.* **28**:944, 1931.

FRACTURE OF THE SKULL IN CHILDREN*

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This report is based on a study of 80 cases of fracture of the skull in patients under 12 years of age admitted to the Children's Memorial Hospital during the years from 1913 to 1930, inclusive. It includes all proved cases of fracture of the skull, the records of which are available, in the charity service during that period. All the cases included were proved to be cases of fracture of the skull by roentgen examination or by roentgen examination and operation at which the fracture was actually demonstrated. All doubtful cases have been excluded from this report because of the great confusion that exists in medical literature regarding the prognosis and treatment in fracture of the skull. It is believed that by basing this study only on proved cases definite conclusions may be drawn. It is probable that some cases of fracture of the skull were in the hospital that are not included in this report, as it has been shown by Apfelbach and LeCount,¹ Troell and Holmström,² Kulcke,³ Moody,⁴ Bissell and LeCount,⁵ McClure and Crawford⁶ and others that a fracture of the skull is often not demonstrable by means of a roentgenogram.

ETIOLOGY

Table 1 gives the sex and age of the patients and the traumatic agents producing the fractures. Of the 80 patients, 54 (67.5 per cent) were boys, and 26 (32.5 per cent) were girls. The youngest patient

* Submitted for publication, April 28, 1931.

* From the Surgical Service of Dr. A. H. Montgomery at the Children's Memorial Hospital.

1. Apfelbach, C. W., and LeCount, E. R.: Pathologic Anatomy of Traumatic Fractures of Cranial Bones and Concomitant Brain Injuries, *J. A. M. A.* **74**:501 (Feb. 21) 1920.

2. Troell, Abraham, and Holmström, P.: The Importance of Roentgen Examinations in the Diagnosis of Fractures of the Skull, *Ann. Surg.* **84**:202 (Oct.) 1927.

3. Kulcke: Ein Beitrag zur Frage der Therapie der Schadelbasisfracturen, *Deutsche Ztschr. f. Chir.* **166**:274 (Sept.) 1921.

4. Moody, W. B.: Traumatic Fracture of the Cranial Bones, *J. A. M. A.* **74**:511 (Feb. 21) 1920.

5. Bissell, W. W., and LeCount, E. R.: The Relative Frequency of the Various Causes of Coma, *J. A. M. A.* **68**:500 (Feb. 17) 1917; A Consideration of the Relative Frequency of the Various Forms of Coma, *ibid.* **64**:1041 (March 27) 1915.

6. McClure, R. D., and Crawford, A. S.: The Management of Craniocerebral Injuries, *Arch. Surg.* **16**:451 (Feb.) 1928.

was aged 46 days and the oldest 11 years; the average age was 4 years. The groups from 9 to 10 and from 10 to 11 years old had the smallest number of patients injured, there being only 2 patients in each of these groups. The group from 3 to 4 years had the greatest number injured, there being 13 patients in this group. This is the age at which walking is uncertain and the gait unsteady, and at which falls are frequent; consequently, at this age fracture of the skull is common.

Falls were the most frequent causative agent, producing 62.5 per cent of the injuries. Many of the falls were from apparatus on playgrounds. Automobiles caused the injury in 25 per cent of the patients. McClure and Crawford⁶ reported that 68.7 per cent of their patients under 10 years of age were injured by automobiles. Despite repeated laws made to control traffic, the automobile continues to be a large

TABLE 1.—*Traumatic Agents According to Age and Sex*

Age, Year	Auto- mobile		Fall		Blow		Street Car		Gun- shot		Struck by Bicycle		Crushed		Not Stated		Total		Both Sexes
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
46 days to 1 year.....	1	1	1	2	1	3
1 to 2.....	5	3	1	6	3	9
2 to 3.....	2	..	5	4	1	8	4	12
3 to 4.....	3	..	6	4	9	4	13
4 to 5.....	2	1	2	1	..	1	4	3	7
5 to 6.....	1	..	4	1	6	0	6
6 to 7.....	1	2	5	1	1	6	4	10
7 to 8.....	3	1	3	1	7	1	8
8 to 9.....	..	3	3	1	1	4	4	8
9 to 10.....	1	1	1	1	1	2
10 to 11.....	1	1	1	1	2
Totals.....	13	7	35	15	1	1	2	1	1	..	1	1	1	1	54	26	80
Totals, both sexes.....	20		50		2		3		1		1		1		2		80		
Percentage of 80 cases.	25		62.5		2.5		3.7		1.2		1.2		1.2		2.5		100		

factor in producing fracture of the skull. Children at the unsteady age of from 3 to 4 years, as noted in the foregoing paragraph, often become separated from the parent or attendant accompanying them on the street and walk into the path of a passing automobile, and a fracture of the skull is the result. Among the more infrequent causes were blows, street car and bicycle accidents, crushing injuries and gunshots.

LOCATION AND EXTENT OF FRACTURES

Table 2 classifies the fractures as to whether they were linear and as to whether they were depressed or elevated; also as to what bone or bones were fractured. The parietal bone was fractured more frequently than any other. In this series 45 patients showed a fracture of the parietal bone, 17 of this bone alone and 28 of the parietal bone and of other bones of the skull. Fracture of the frontal bone was next in frequency; there were 35 patients in this group, 17 with a

fracture of the frontal bone only and 18 with a fracture of the frontal bone and of other bones of the skull. No patient with a fracture of the frontal bone acquired meningitis or abscess of the brain, although this is frequently reported subsequent to a fracture extending into the frontal sinus. Eight patients had depressed fractures. One of these fractures was not visible in the roentgenogram, but was found at operation. Three patients had definite elevation of the fragment, a condition rarely described in the literature. None of them was operated on, and all recovered. Sixty-three patients (78.7 per cent) had a fracture of the vault alone, 8 (10 per cent) of the base alone and 8 (10 per cent) of both vault and base; the location of the fracture in 1 patient (1.2 per cent) was not stated. Only 2 patients (2.5 per cent) had separation of the sutures, a condition frequently described in the literature on fracture of the skull in children. It would seem that the percentage

TABLE 2.—*Classification of Fractures*

Bone Fractured	Linears			Depressed			Elevated	Bilateral	Total
	Right Side	Left Side	Not Stated	Right Side	Left Side	Not Stated			
Frontal.....	12	7	1	1	1	1	..	1	23
Parietal.....	6	4	5	1	1	1	2	..	18
Occipital.....	8	8
Temporal.....	1	1	2
Frontoparietal.....	3	5	1	1	..	1	11
Frontotemporal.....	1	1
Parieto-occipital.....	1	4	3	8
Parietotemporal.....	1	3	1	1	6
Fronto-ethmoid.....	1	1
Temporo-occipital.....	2	2
Frontoparieto-occipital.....	2	2	1	5
Temporoparieto-occipital.....	1	1
Frontoparietotemporal.....	1	..	1

of basal fractures in children is not so high as that of basal fractures in adults. Many of the basal fractures in adults are fractures by contre-coup, but it is doubtful whether the percentage of contre-coup fractures in children is as high as it is in adults. Hence, the percentage of basal fractures in children would be less. Among the various investigators who have reported series in adults, Apfelbach and LeCount¹ found fracture of both vault and base in 92 per cent of their patients; Besley,⁷ in 34 per cent. The average age of 68.7 per cent of Besley's patients was over 30 years. Stewart⁸ reported basal fractures in 34 per cent and fractures of the vault in 66 per cent of his patients, the ages of whom averaged 36 years. On the other hand, Beekman⁹ reported that 74

7. Besley, F. A.: A Contribution to the Subject of Skull Fractures, J. A. M. A. 66:345 (Jan. 29) 1916.

8. Stewart, J. W.: Fractures of the Skull, J. A. M. A. 77:2030 (Dec. 24) 1921.

9. Beekman, Fenwick: Head Injuries in Children, Ann. Surg. 87:355 (March) 1928.

per cent of his patients, all of whom were under 13 years of age, had basal fractures.

The lengths of the fractures in 58 patients were measured as seen in roentgenograms. The longest fracture, which completely encircled the vault, was 36 cm.; the shortest was 0.6 cm.; the average length was 8.4 cm. Eleven patients were examined roentgenographically a second time. The shortest period of time between the first and the second examination was 282 days, the longest period was 6 years and 12 days, and the average interval was 647 days. In every patient except 1, the fracture had completely closed at the second examination, and there was no evidence of thickening or of callus. In the patient whose fracture had not completely healed, as shown by the roentgenogram, the fracture extended entirely around the vault, as noted, and was plainly visible 610 days after the injury. Stewart¹⁰ stated that there is little formation of callus following fracture of the skull, and that all roentgenographic evidence of fracture of the skull in a child may disappear within from 6 to 8 months. He also stated that in an adult a simple linear fracture may remain visible for 3 years, and that if there is much separation, the defect may remain visible for from 3 to 5 years.

In the cases analyzed here, there seemed to be no more tendency for a fracture of the vault to extend into the base than to extend in any other direction. This is the opposite of what is true for adults, in whom the fracture has a great tendency to follow between the heavy arches into the base, as described by Apfelbach and LeCount.¹

SYMPTOMS

Many of these patients arrived at the hospital in police ambulances only a few minutes after they had been injured. Sixty-six (82.5 per cent) entered the hospital on the same day that they were injured. The remaining 14 (17.5 per cent) entered from 1 to 100 days after injury.

Thirty-two patients (40 per cent) were unconscious immediately following the accident, and 12 (15 per cent) were unconscious on entrance into the hospital. Eighteen (22.5 per cent) regained consciousness between the time of injury and the time of entrance into the hospital.

Sixty-eight (85 per cent) had a visible laceration, hematoma or contusion of the head. Headache was present in 17 patients (21.2 per cent), dizziness in 9 (11.2 per cent) and vomiting in 51 (63.7 per cent), with bloody vomitus in 18 (22.5 per cent). From these percentages, vomiting would seem to be an important symptom of fracture

10. Stewart, W. H.: The Time Factor in the Disappearance of Roentgenographic Evidence of Fractures of the Skull, *Brit. J. Radiol.* **30**:399 (Nov.) 1925.

of the skull in children. When vomiting follows an injury to the head, one should immediately suspect that there is a fracture of the skull.

In 66 patients (82.5 per cent) the pupils were equal, and in 11 (13.7 per cent) they were unequal. The right pupil was larger in 6 patients; the left, in 4, and in 1 it was not stated which was larger. In 2 patients (2.5 per cent) both pupils were fixed and dilated; these patients died. Phelps¹¹ reported that in patients with fixed and dilated pupils the mortality was 100 per cent. Stewart⁸ also noted a mortality of 100 per cent in 53 patients with fixed and dilated pupils. In the present series there were 73 patients (91.2 per cent) in whom the pupils reacted to light, and 4 (5 per cent) in whom they did not; the pupillary reactions of 3 patients were not stated. In most of the patients, because of their age, the test for the reaction to accommodation was unsatisfactory.

Examination of the eyegrounds was not considered of much importance, except in patients whose severe symptoms lasted several days. The fundi were examined in 6 patients. Three had normal fundi; 1 had a hazy disk, 1 had definite papilledema and 1 had a retinal hemorrhage. All recovered. Jackson¹² intimated that examination of the eyegrounds is of little value in fracture of the skull. Moorhead and Weller¹³ stated that the importance of choked disk is much overrated. Speed¹⁴ found that examination of the eyegrounds was of little prognostic value in early cases. Johnson¹⁵ examined the fundi in 154 patients with cranial and intracranial injuries and noted changes only in 4. In contrast, Cushing¹⁶ thinks that examination of the eyegrounds is of much value, and Shere,¹⁷ Maes (quoted by Crawford¹⁸) and Haines¹⁹

11. Phelps, Charles: An Analytical and Statistical Review of 1,000 Cases of Head Injury, *Ann. Surg.* **49**:511 (April 1) 1909.

12. Jackson, Harry: The Management of Acute Cranial Injuries by the Early Exact Determination of Intracranial Pressure and Its Relief by Lumbar Drainage, *Surg., Gynec. & Obst.* **34**:494 (April) 1922.

13. Moorhead, J. J., and Weller, Walter: Fractures of the Skull in Children, *Ann. Surg.* **74**:72 (July) 1921.

14. Speed, Kellogg: Gunshot Fractures of the Skull, *J. A. M. A.* **68**:1299 (May 5) 1917.

15. Johnson, J. G. W.: Cranial and Intracranial Injuries, *Internat. Clin.* **2**:266 (June) 1926.

16. Cushing, Harvey: Subtemporal Decompression Operations for the Intracranial Complications Associated with Bursting Fractures of the Skull, *Ann. Surg.* **47**:641 (May) 1908.

17. Shere, O. M.: Indications for Operative Treatment in Cranial Fractures, *Colorado Med.* **17**:9, 1920.

18. Crawford, L. B.: Some Fractures of the Base Treated by Repeated Spinal Punctures, *New Orleans M. & S. J.* **74**:374, 1921-1922.

19. Haines, W. D.: Fractures of the Skull, *Ohio State M. J.* **15**:281 (May) 1918.

think likewise. Eagleton²⁰ said that such an examination may show moderate increase of the intracranial pressure in fracture of the skull when no other symptoms are present, but he had never seen a typical choked disk in a patient with fracture of the skull.

Only 2 patients had paralysis of the extrinsic muscles of the eyes, three had nystagmus, and one had diplopia.

Nineteen patients (23.7 per cent) had bleeding from the nose. Two of these had only a basal fracture, 14 had a fracture only of the vault, and 3 had a fracture of both the base and the vault. It is significant that fracture of the vault should cause such a high incidence of nasal hemorrhage. Twelve patients (63.5 per cent) of the 19 who had nasal hemorrhage had a fracture of the frontal bone. Hence, nasal hemorrhage following an injury to the head should cause one to suspect that there is a fracture of the frontal bone. Eleven patients (14 per cent) had bleeding from the ears, 9 from the left ear alone, none from the right alone and 2 from both ears. One of these had a basal fracture, 7 a fracture of the vault, and 2 a fracture of both the base and the vault. The nature of the fracture in 1 was not stated. In 5 of the patients who had bleeding from the left ear, the left side of the skull was fractured; in 2 who had bleeding from the right ear, and in 3 who had bleeding from the left ear, the right side was fractured. The location of the fracture in 3 patients with bleeding from the left ear was not stated. From the statistics of aural hemorrhage no conclusion can be drawn as regards the bone fractured. Fourteen patients (17.5 per cent) had bleeding from the mouth; 3 of these had a fracture of the base, 9 of the vault and 2 of both the base and the vault.

The blood pressure was recorded 45 times for 22 patients. The highest systolic blood pressure was 152 mm. of mercury, the lowest 80 and the average 106. The highest diastolic pressure was 92 mm. of mercury, the lowest 7 and the average 59. The systolic pressure of one of the patients who died was 96 and the diastolic 70. The blood pressure of the other patient who died was not recorded. The readings of the blood pressure of patients whose pressure was taken more than once tended to be lower the longer the patient remained under observation. It would seem that in accordance with the conclusion of Vance,²¹ no definite prognostic conclusion could be drawn from the blood pressure of these patients.

The muscle reflexes were recorded for 71 patients (88.7 per cent). In 4 patients all the reflexes were increased. All reflexes were increased on the right side twice, and the right knee reflex was increased twice. The reflexes were absent on the left side once. The right knee jerk was

20. Eagleton, W. P.: Fracture of the Skull, *Arch. Surg.* **3**:140 (July) 1921.

21. Vance, B. M.: Fractures of the Skull, *Arch. Surg.* **14**:1023 (May) 1927.

absent twice and sluggish once; the left knee jerk was absent once. The abdominal reflexes were recorded as absent twice. Babinski's sign was positive 3 times on the right and 3 times bilaterally. Kernig's sign was positive once on the right. All reflexes were absent in 2 patients (one of these died; the other recovered). There was a total of 12 patients (15 per cent) with abnormal reflexes and 68 (85 per cent) with normal reflexes. These statistics indicate that normal reflexes frequently accompany fracture of the skull in children.

The highest temperature of any patient was 105 F., taken rectally; the lowest was 96 F. The lowest average temperature attained by all patients was 95.2 F. (obtained by averaging the lowest temperatures attained by the patients individually). The highest average temperature was 101.4 F., taken rectally (obtained by averaging the highest temperatures attained by the patients individually). The general average temperature was 100.1 F., taken rectally. The lowest rectal temperatures attained by the patients individually in the first 24 hours after admission were averaged, and the average was found to be 98.8 F. There were 8 patients whose temperatures did not fall below 99.6 F. rectally in the first twenty-four hours after admission. This is at variance with the observations of Hipsley,²² who stated that the temperature is always subnormal in fracture of the skull. It also shows that not all the patients are in a state of severe shock on admission. In Besley's⁷ fatal cases the average temperature was 102 F. Courtney²³ held that the prognosis is bad if the temperature is over 102 F., and that the temperature is the most important sign in intracranial traumatism. Eight patients of the series had temperatures over 102 F., taken by mouth (103 F., rectally); seven of these recovered. No definite prognostic conclusions can be drawn from the temperature in these cases, unless it is that cases marked by high temperatures (over 102 F., taken rectally) are not usually fatal in children, as they often are in adults.

In this series, if the patient was perfectly conscious and apparently normal except for the fracture, it was not deemed necessary to record the pulse and the temperature every 15 minutes, as is frequently recommended. The highest pulse rate recorded was 180 per minute, the lowest was 50, and both of the patients recovered. The highest average pulse rate (obtained by averaging the highest pulse rates attained by the patients individually) was 133. The lowest average pulse rate was 79. The general average pulse rate was 106. Regarding the pulse rates of the two patients who died, the pulse of one was constantly imper-

22. Hipsley, P. L.: Fracture of the Skull in Children, *M. J. Australia* 1:5 (Jan. 3) 1925.

23. Courtney, J. W.: The Temperature as a Valuable Guide to Diagnosis, Prognosis and Surgical Treatment in Cranio-Cerebral Traumatisms, *Boston M. & S. J.* 177:511, 1917.

ceptible, and the pulse rate of the other was not recorded. Twelve patients (15 per cent) had a pulse rate of over 150, and all of these recovered. Hence, a high pulse rate (over 150) would not seem to be a bad sign in fracture of the skull in children. As stated previously, the lowest pulse rate recorded was 50; the pulse rate in fracture of the skull in adults often is much lower than this.

The highest respiration rate attained by any patient was 60, the lowest 15 per minute. The highest average respiration rate (obtained by averaging the highest respiration rates attained by the patients individually) was 34; the lowest average was 19. The general average was 26.5.

COMPLICATIONS

Thirteen patients had fracture of one or more bones in addition to fracture of the skull. The other bones fractured with the number of cases, were: femur, 5; humerus, 2; maxilla, 1; palatinum, 1; forearm, 1; clavicle, 1; tibia, 1, and metatarsal, 1. Also, there were other complications, as follows: tearing of the spinal nerve roots of the brachial plexus, 1; pneumonia, 1; pleurisy, 1; infected wounds, 2, and otitis media, 3. The symptoms that developed as a direct result of the fracture of the skull, with the number of cases, were: flaccid paralysis of the right side of the body, 2; weakness of the right arm and the right leg, 1; deviation of the tongue to the right, 1; generalized convulsions, 1; twitching of the hand, 1; twitchings of facial muscles, 3; twitching of muscles of the arm and leg, 1, and twitching of the eye, 1. No patient died from a complication or from a concomitant injury.

DIAGNOSIS

Lumbar puncture was performed 14 times on 13 patients. The pressure of the spinal fluid was recorded as increased 10 times and as normal twice; in 2 instances the amount of pressure was not stated. The cerebrospinal fluid was bloody 9 times and clear 3 times; in 2 cases the character of the fluid was not stated.

Stewart,⁸ Hipsley,²² Boyd,²⁴ Eagleton,²⁰ Shere,¹⁷ Carter,²⁵ Moorhead and Weller¹³ and Haines¹⁹ are in favor of lumbar puncture for diagnosis, while Sachs²⁶ opposes it. Cushing²⁷ stated that he was in

24. Boyd, William: *The Cerebrospinal Fluid*, New York, The Macmillan Company, 1920, p. 33.

25. Carter, B. N.: *Diagnosis and Treatment of Fractures of the Skull as Developed in the Cincinnati General Hospital*, *Ann. Surg.* **83**:182 (Feb.) 1926.

26. Sachs, Ernest: *Diagnosis and Treatment of Head Injuries*, *J. A. M. A.* **81**:2159 (Dec. 29) 1923.

27. Cushing, Harvey: *Some Experimental and Clinical Observations Concerning States of Increased Intracranial Tension*, *Am. J. M. Sc.* **124**:374 (Sept.) 1902.

doubt as to how much stress to place on lumbar puncture for diagnosis. Schoenbeck²⁸ collected 71 cases in which death occurred following lumbar drainage; in 69 of these at necropsy a tumor or other acute or chronic disease of the brain was found. Hence, unless a history of symptoms of a disease of the brain antedating the injury to the head has been obtained, lumbar puncture seems to be almost without danger. However, as correctly pointed out by Besley,⁷ there is sufficient danger so that puncture should not be done if a diagnosis can be made by physical examination, roentgen examination and other means. Little use was made of lumbar puncture in this series for the reason stated, and the diagnosis could usually readily be made without it.

There was no case in which the diagnosis of epidural hemorrhage was made. Vance²¹ reported 2 cases of epidural hemorrhage, occurring in patients between 10 and 20 years. Epidural hemorrhage is less frequent in children than in adults, because the dura is more adherent to the skull in children, while in adults it is loosely adherent and allows a clot to form readily between it and the skull. There was no case with a diagnosis of pneumocephalus, as described by Rand.²⁹ One patient had a fracture of the frontal sinus, as described by Teachenor;³⁰ infection of the brain did not develop, and the child recovered.

PROGNOSIS

In cases of fracture of the skull the prognosis is much better for children than for adults, for the following reasons: 1. The shock of a surgical operation is less in younger people than in older ones (Brophy³¹). 2. The edges of the bones of the vault of the skull in childhood are connected by a membrane and are comparatively movable, and for this reason the blood vessels that lie directly beneath the fracture are not so readily torn and the brain is not so seriously injured (Piersol³²). 3. The furrows of the skull in which the blood vessels lie are not so deep in children. 4. Bones in children are more elastic, and there is more tendency toward greenstick fracture. 5. The sutures are less dense and therefore interrupt the transmission of violence to a greater

28. Schoenbeck, O.: Die Gefahren der Lumbalpunktion, *Arch. f. klin. Chir.* **107**:309, 1915-1916.

29. Rand, C. W.: Traumatic Pneumocephalus, *Arch. Surg.* **20**:934 (June) 1930.

30. Teachenor, F. R.: Intracranial Complications of Fracture of Skull Involving Frontal Sinus, *J. A. M. A.* **88**:987 (March 26) 1927.

31. Brophy, W. T.: *Oral Surgery*, Philadelphia, P. Blakiston's Son & Company, 1915, p. 609.

32. Piersol, G. A.: *Human Anatomy*, ed. 9, Philadelphia, J. B. Lippincott Company, 1930.

degree. 6. Basal fracture is less common because the heavy arches³³ at the base of the skull are not so pronounced in children; hence, the fracture is not so readily radiated into the base, and because the vertebral column in children is less rigid and does not transmit force to the skull so violently in cases of vertebral injury. 7. Hipsley²² said that the associated injury to the brain in children is less because the subarachnoid cavity is dilated and acts as a water cushion between the anterior and middle fossae and between the middle and posterior fossae. Levinson,³⁴ however, stated that there is less cerebrospinal fluid during the first twenty-four hours in the new-born child than in older children. 8. As children have a lower cerebrospinal fluid pressure than adults, the brain is better protected against the force producing the fracture.

Two (2.5 per cent) of the 80 patients died. This mortality is extremely low, as is shown in a comparison of the following statistics: Carter²⁵ reported 41 cases occurring in patients between the ages of 1 and 10, in which there was a mortality of 14.6 per cent, and 29 cases occurring in patients between the ages of 10 and 20, in which the mortality was 13.7 per cent. Harris and Nissen³⁵ reported 56 cases in patients aged from 1 to 10, with 24 deaths (42.8 per cent). Twenty-two of these patients were operated on; 7 died (31.8 per cent); of 34 not operated on, 17 lived and 17 died (a mortality of 50 per cent). Johnson¹⁵ reported 20 cases in patients aged from 1 to 10, 3 of whom died (15 per cent). Rand and Nielsen³⁶ reported 12 cases in patients aged from 1 to 10, with 1 death (8.3 per cent), and 22 cases in patients aged from 10 to 20, with 5 deaths (22.7 per cent). Hipsley²² reported 27 cases in patients aged from 1 week to 12 years, with 2 deaths (7.4 per cent). Beekman⁹ reported a mortality of 13 per cent in 214 cases of fracture of the skull in children under 13 years of age. Moorhead and Weller¹³ reported that in 100 cases in children aged from 3 months to 16 the total mortality was 26 per cent. In 12 patients that were operated on the mortality was 33.3 per cent. Mixer³⁷ reported a mortality of 54.1 per cent in 301 patients, including both children and adults. Brown and Strecker³⁸ reported 100 cases in children and adults,

33. LeCount, E. R.: *The Pathology of Skull Fractures*, Northwest Med. **18**: 205, 1919; Apfelbach and LeCount (footnote 1).

34. Levinson, A.: *Cerebrospinal Fluid in Infants and in Children*, Am. J. Dis. Child. **36**:798 (Oct.) 1928.

35. Harris, C. T., and Nissen, H. A.: *A Series of Fractured Skulls from the Surgical Records of the Boston City Hospital 1902-1917*, Boston M. & S. J. **177**: 870 (Dec. 20) 1917.

36. Rand, C. W., and Nielsen, J. M.: *Fractures of the Skull*, Arch. Surg. **2**:434 (Sept.) 1925.

37. Mixer, W. J.: *Fractures of the Base of the Skull at Massachusetts General Hospital*, Boston M. & S. J. **177**:518 (Oct. 11) 1917.

38. Brown, H. P., Jr., and Strecker, E. A.: *Some Observations on the Treatment of Fracture of the Skull*, Ann. Surg. **79**:198 (Feb.) 1924.

with 26 deaths (26 per cent); of 17 patients operated on, 6 died, and of 83 not operated on, 20 died. McCreery and Berry³⁹ reported 33 deaths in 62 cases in adults that were operated on (53 per cent mortality). They had a total mortality of 39 per cent in 204 cases. Shere¹⁷ reported that 67 per cent of his patients (ages not stated) were operated on, with a mortality of 48.8 per cent, and that 33 per cent were not operated on, with a mortality of 59 per cent. Selberg⁴⁰ stated that the mortality in fracture of the skull (ages of patients not stated) approaches 50 per cent. Crawford¹⁸ reported 10 patients (ages not stated) treated by lumbar puncture; all recovered.

The prognosis is bad when the pupils are fixed and dilated and when all the reflexes are absent. A high temperature (i. e., over 102 F.), unless it is continued for a long period of time, does not seem to be a bad prognostic sign in children. As noted, 7 of the patients who had temperatures over 102 F. recovered. The injury to the brain is much more important than the fracture of the skull. Many patients die from injuries of the brain in cases in which no fractures can be demonstrated at necropsy. Hence, the prognosis depends chiefly on the extent of the pathologic process in the brain.

TREATMENT

Since Weed and McKibbin⁴¹ showed that the bulk of the brain and the pressure of the cerebrospinal fluid can be reduced by intravenous injection of hypertonic salt solution, and since Foley⁴² showed that the flow of cerebrospinal fluid through the choroid plexus is reversed in direction by intravenous or intraduodenal administration of salt, these methods have been extensively used in fracture of the skull.

Hypertonic salt solution given intravenously, as described by Weed and McKibbin,⁴¹ was recommended by Newell,⁴³ Johnson,¹⁵ Keegan⁴⁴ and Grant.⁴⁵ On the other hand, Rand and Nielsen³⁶ and Sachs²⁶

39. McCreery, J. A., and Berry, F. B.: A Study of 520 Cases of Fracture of the Skull, *Ann. Surg.* **88**:890 (Nov.) 1928.

40. Selberg, F.: Nachuntersuchungen an Schadelbrüchen, *Deutsche med. Wchnschr.* **54**:2099 (Dec. 14) 1928.

41. Weed, L. H., and McKibbin, P. S.: Pressure Changes in Cerebrospinal Fluid Following Intravenous Injections of Solutions of Various Concentrations, *Am. J. Physiol.* **48**:512 (May) 1919; Experimental Alteration of Brain Bulk, *ibid.* **48**:531 (May) 1919.

42. Foley, F. E. B.: Alteration in the Currents and Absorption of Cerebrospinal Fluid Following Salt Administration, *Arch. Surg.* **6**:587 (March) 1923.

43. Newell, E. T.: Diagnosis and Treatment of Fractures of the Skull, *J. South Carolina M. A.* **25**:461 (July) 1929.

44. Keegan, J. J.: When to Operate and When Not to Operate in Fractures of the Skull, *Nebraska M. J.* **10**:333 (Sept.) 1925.

45. Grant, F. C.: Chronic Subdural Hematoma, *Ann. Surg.* **86**:485 (Oct.) 1927.

said that they were not in favor of hypertonic salt solution given intravenously. Haines¹⁹ stated that hypertonic salt solution should not be injected during the period of shock, because it increases the blood pressure. The intravenous injection of dextrose was recommended by Newell.⁴³ Johnson¹⁵ and Rand and Nielsen³⁶ were in favor of magnesium sulphate, given either as an enema or orally. Opposing this view, Connors⁴⁶ saw no benefit from 50 per cent magnesium sulphate given as an enema.

Lumbar puncture was done on 13 patients—whether for diagnostic or therapeutic purposes was not definitely stated. One patient that had a lumbar puncture died, the puncture being made while the patient was in a state of extreme shock, when it should not have been done, as pointed out by Munroe⁴⁷ in relation to extreme shock in the new-born infant. Phelps,¹¹ Carcassonne,⁴⁸ Harris and Nissen,³⁵ Elder,⁴⁹ Newell,⁴³ Bowen and Van Schaick,⁵⁰ Rand and Nielsen,³⁶ Hipsley,²² Jackson,¹² Stewart,⁸ Boyd,²⁴ Munroe,⁴⁷ Eagleton,²⁰ Keegan,⁴⁴ Crawford,¹⁸ Ferry⁵¹ and Johnson¹⁵ favored lumbar puncture in treatment. Some depend on accurate measurement of the pressure of the spinal fluid to determine the amount of fluid to withdraw and others merely estimate it. There seems to be no uniform rule.

There is a marked disagreement as to what constitutes normal pressure of the cerebrospinal fluid as measured at lumbar puncture. Waitz⁵² held that in the new-born infant it is zero; Munroe⁴⁷ placed it at from 2 to 6 mm. of mercury, Sidbury⁵³ at from 2 to 5 mm. and Levinson³⁴ at from 1 to 6 mm. Quincke⁵⁴ found the normal pressure

46. Connors, J. F.: The Treatment of Skull Fractures, *Tr. Am. S. A.* **45**:426, 1927.

47. Munroe, Donald: Cerebrospinal Fluid Pressure in the New-Born, *J. A. M. A.* **90**:1688 (May 26) 1928.

48. Carcassonne: Fracture de la base du crâne traitée par ponction lombaire, *Lyon méd.* **148**:715, 1929.

49. Elder, H. M.: Fracture of the Skull of a Child Treated by Repeated Puncture of the Cisterna Magna, *Canad. M. A. J.* **15**:1248, 1925.

50. Bowen, Frederick; and Van Schaick, Harold D.: Spinal Puncture as Treatment in Cranial Fractures, *J. Florida M. A.* **12**:310 (May) 1926.

51. Ferry, G.: Contribution à l'étude du diagnostic et du traitement des fractures de la base du crâne, *Rev. de chir., Paris* **61**:117, 1923.

52. Waitz, R.: Le liquide céphalorachidien du nouveau-né, *Rev. franç. de pédiat.* **4**:1, 1928.

53. Sidbury, J. B.: The Importance of Lumbar Puncture in Intracranial Hemorrhage of the New-Born, *Arch. Pediat.* **37**:545 (Sept.) 1920.

54. Quincke, H.: Ueber den Druck in Transsudaten, *Deutsches Arch. f. klin. Med.* **21**:453, 1887; Ueber die therapeutischen Leistungen der Lumbalpunktion, *Therap. Monatsh.* **28**:469 (July) 1914; Die diagnostische und therapeutische Bedeutung der Lumbalpunktion, *Deutsche med. Wchnschr.* **31**:1825 (Nov. 16) 1905.

in children to be from 40 to 60 mm. of water. Falkenheim and Naunyn⁵⁵ found it to be from 50 to 500 mm. of water in children aged from 1 month to 1 year. Levinson⁵⁶ found it to be from 45 to 90 mm. of water in children lying and from 150 to 230 mm. in children sitting. Phelps¹¹ stated that the normal pressure (age not stated) is from 50 to 100 mm. of water. Boyd²⁴ gave the normal pressure as from 90 to 150 mm. of water (age not stated), and stated further that even if the medulla is forced into the foramen magnum, there may be no increase in the spinal pressure even with high intracranial pressure. Howe⁵⁷ stated that the intracranial pressure is roughly equal to the venous pressure. Levinson⁵⁸ stated that if more than 10 cc. of fluid can be removed at a single sitting, or if there is a flow of over 10 drops per minute, it indicates an increase in the amount of pressure. Munroe⁴⁷ removed as much as 90 cc. of fluid in one case. He stated that the spinal pressure in new-born infants who lived averaged the same as that in those who died; but that in adults, the pressure was $2\frac{1}{2}$ times greater in those whose fractures were fatal than in those whose fractures were not. Cushing⁵⁹ stated that the spinal pressure should equal the venous pressure, or about 4 mm. of mercury (no reference was made to age).

Connors,¹⁶ Dandy⁶⁰ and Sachs²⁶ did not favor lumbar puncture in the treatment for fracture of the skull. They expressed the belief that it may do harm and that injury to the base of the brain or even sudden death may result from it. Eagleton,²⁰ McClure and Crawford,⁶ Elder⁴⁹ and Johnson¹⁵ favored cysternal or ventricular puncture in some cases.

Therapeutic lumbar puncture should not be done as a matter of routine in cases of fracture of the skull in children. For example, if a patient is perfectly conscious, has no evidence of intracranial pressure, as shown by the pulse, the blood pressure, the respiration or other physical signs, puncture should not be made. With signs of increasing pressure, it may be carefully done, the fluid being drained off very slowly and the drainage being discontinued if any untoward symptoms develop.

55. Falkenheim, H., and Naunyn, B.: Ueber Hirndruck, Arch. f. exper. Path. u. Pharmacol. **22**:261, 1887.

56. Levinson, Abraham: Cerebrospinal Fluid, ed. 3, St. Louis, C. V. Mosby Company, 1929.

57. Howe, H. S.: Physiologic Mechanism for the Maintenance of Intracranial Pressure, Arch. Neurol. & Psychiat. **20**:1048 (Nov.) 1928.

58. Levinson, Abraham: Cerebrospinal Fluid, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 96.

59. Cushing, Harvey: Some Experimental and Clinical Observations Concerning States of Increased Intracranial Tension, Am. J. M. Sc. **124**:376 (Sept.) 1902.

60. Dandy, Walter: Injuries to the Head, J. M. Soc. New Jersey **27**:91 (Feb.) 1930.

If tapping the spinal fluid does not relieve the symptoms of pressure, surgical decompression may be done. Surgical decompression was done in 7 patients (8.7 per cent), 1 of whom died. Two were operated on for depressed fractures; the depression was elevated in the one, and bony fragments were removed in the other. Seven patients (8.7 per cent) had depressed fractures on whom operation was not done. All of these recovered. This is in accord with Beekman,⁹ who did not think it necessary to operate on all patients with depressed fractures. The 4 patients with elevated fractures were not operated on, and all recovered. Two patients were operated on who had no depression. One was operated on for removal of a bullet; this patient recovered. One patient operated on was found to have no pathologic condition of the brain; this patient died.

Wagner⁶¹ in 1889 first introduced the flap of bone and soft tissue in operations on the skull: the omega-shaped flap is turned down and replaced at the close of the operation. It leaves little defect. Cushing's¹⁶ subtemporal decompression tends to prevent hernia cerebri, because it is beneath the temporal muscle. Jackson¹² considered that the decompression advised by Cushing does not adequately relieve the pressure on the medulla, probably because the pressure is subtentorial and the operation supratentorial. Vance²¹ found the pons actually flattened by being pushed against the basilar process when both subdural spaces were distended with extravasated blood, which shows that pressure above the tentorium may be transmitted to the base of the brain. It is logical that if most of the injury is above the tentorium, most of the edema of the brain will be there; hence the decompression above the tentorium would be most beneficial. Cerebellar injuries (i. e., those below the tentorium) are not so common as those above the tentorium (i. e., cerebral). There is at times a question as to the actual amount of edema of the brain. In the 512 necropsies of Vance²¹ no death was found to have resulted from edema of the brain. He did not find the marked swelling of the brain that LeCount and Apfelbach found. Courtney²³ stated that trephining for the relief of edematous compression in adults is for the most part a fruitless expedient. Perkins (quoted by Crawford¹⁸) stated that the end-results of decompression are poor, and that paralysis and imbecility may occur.

Pollak⁶² thought that comminuted fractures of the vault should have a thorough exploration. Newell⁴⁸ considered a pulse rate of 50 or less sufficient indication for operation. Eagleton²⁰ stated that a diastolic pressure below 55 is a contraindication for operation because

61. Wagner, W.: Die temporäre Resektion des Schädeldachs an Stelle der Trepanation, *Zentralbl. f. Chir.* **16**:833 (Nov. 23) 1889.

62. Pollak, A. W.: Unrecognized Fractures of the Skull in Infants and Children, *M. J. & Rec.* **119**:65 (April 2) 1924.

the patient is in a state of shock. Keegan ⁴⁴ and McCreery and Berry ³⁹ thought that a patient suffering from shock should not be operated on. In this group the patient who died was operated on while in this condition. This, beyond doubt, contributed to the fatality.

Mixer ³⁷ said that he removes the loose and depressed fragments of bone. Speed ¹⁴ said that in gunshot fractures he removes the loose fragments of bone. On the other hand, Cushing ⁶³ said that he is inclined to replace the fragments; however, he did not think defects left in the skull are injurious unless accompanied by an underlying lesion of the dura. Hanson and his associates ⁶⁴ held that moderate-sized defects left in the skull by operation should be closed, and he reported good results from closing the defect with costochondral cartilage. Large defects left in a skull, even that of a young child, will not always close, and may later be a source of serious consequences. The defect is always exposed to trauma. It may, however, be protected with a metal cap, as described by Seifert. ⁶⁵ All large bony fragments, except those definitely contaminated, should be replaced, even if completely loosened from all tissue at the time of operation.

In children, small depressions, areas of bone only slightly below the surface of the skull and depressions involving the nasal sinuses or the sinus sagittalis superior if they produce no symptoms, are often best treated without operation. Also, depressions only of the external table of the skull should be treated conservatively.

As a routine, the patients on whom this study is based were kept in bed for 4 weeks. The shortest stay in the hospital was less than 1 day, the longest 100 days, and the average 19 days. In many cases the patient was sent home after having spent less than 4 weeks in the hospital, and instructions were given to keep him in bed at home for a total of 4 weeks. Ice packs were placed on the head on entrance to the hospital. Patients suffering from pain and shock were treated with sedatives. Ether was given to 1 patient for convulsions, and stimulations were given to 1 patient. Tetanus antitoxin was given in compound fractures, deep lacerations or dirty wounds, to 10 patients (12.5 per cent). No medication was administered to 18 (22.5 per cent).

The patients were followed in the dispensary as long as possible. The shortest length of time of observation was less than 1 day; the longest, 6 years and 11 days; the average, 396 days. Sixty-nine patients had completely recovered at the last examination. Nine patients

63. Cushing, Harvey: *Fractures of the Skull*, in Williams, William: *Keen Surgery*, Philadelphia, W. B. Saunders Company, 1919, vol. 3, p. 86.

64. Hanson, A. M.; Hessly, Hanson, and Traeger: *Reconstruction of Internal Table in Cranioplasty*, *Mil. Surgeon* 50:31 (Jan.) 1922.

65. Seifert, E.: *Verlangt die Knochenlücke im Schädeldach einen abesondern Schutz*, *Zentralbl. f. Chir.* 55:910 (April 14) 1928.

(11.2 per cent) had serious sequelae when last examined, which were as follows: epilepsy, 1; paralysis of the left arm and enlargement of the left pupil, 1; weakness of the left leg, 1; the left leg weaker and smaller than the right, 1; a staggering gait, 1; paralysis of the right side of the face and troublesome pulsation in the right ear, 1, and headache, 3.

Healy⁶⁶ stated that in 3.5 per cent of children who are delinquent the condition is due to a trauma to the head. Strecker and Ebaugh⁶⁷ reported 30 cases of injury to the head in children with neuropsychiatric sequelae. Six of these children were improving, but the outlook for the 24 others was discouraging. Reichman⁶⁸ stated that not more than 0.5 per cent of fractures of the skull are followed by epilepsy, and that injury to the left side is more inclined to be followed by epilepsy than injury to the right side. Beekman⁹ stated that less than 5 per cent of patients with fracture of the skull show permanent change; Pollak⁶² thought that many unrecognized cases of fracture of the skull cause disorders of the brain later in life. Johnson¹⁵ reported that 35.3 per cent of his 85 patients had serious sequelae. Stewart⁸ reported that 55 per cent of 255 patients who recovered had unpleasant sequelae. English⁶⁹ reported that in more than 10 per cent of persons with injury to the head there is some mental impairment. Troell and Holmström⁷⁰ reported that 6 per cent of 152 patients were placed on the pay list for invalids in Sweden. Taft and Strecker⁷¹ stated that less than 1 per cent of psychoses probably are due to trauma to the head. Orr⁷² reported a case of jacksonian epilepsy that occurred 12 years after fracture of the skull. Smith and Emera⁷³ reported a case in which death occurred from fracture of the skull 11 years after the injury. Eager⁷⁴ reported a case of psychosis in a patient in the third decade of

66. Healy, William: A Review of Some Studies of Delinquents and Delinquency, *Arch. Neurol. & Psychiat.* **14**:25 (July) 1925.

67. Strecker, E. A., and Ebaugh, F. G.: Neuropsychiatric Sequelae of Cerebral Trauma in Children, *Arch. Neurol. & Psychiat.* **12**:443 (Oct.) 1924.

68. Reichman, V.: Ueber Entstehung und Häufigkeit epileptischer Krämpfe nach Schadelbrüchen, *Deutsche Ztschr. f. Nervenhe.* **96**:260, 1927.

69. English, T. C.: The After Effects of Head Injuries, *Lancet* **1**:485, 1904.

70. Troell, Abraham, and Holmström, Per: Om skallfrakturernas diagnosis, *Svenska läk.-tidning.* **24**:409, 1927.

71. Taft, A. E., and Strecker, E. A.: Psychosis Associated with Trauma of the Head, *Arch. Neurol. & Psychiat.* **14**:658 (Nov.) 1926.

72. Orr, T. G.: Late Results of Skull Fracture, *J. Kansas M. Soc.* **20**:162, 1920.

73. Smith, Sidney; and Emera, Mohammed: A Case of Fracture of the Skull Causing Death After Eleven Years, *Brit. M. J.* **3**:647, 1923.

74. Eager, Richard: Head Injuries in Relation to the Psychosis and Psycho-neurosis, *J. Ment. Sc.* **66**:111 (April) 1920.

life, which perhaps was due to a fall in infancy. Cushing⁷⁵ reported a case of meningeal endothelioma in a patient in whom the symptoms developed 12 years after an injury to the head.

SUMMARY

1. Eighty cases of proved fracture of the skull in children, with 2 deaths (2.5 per cent), are discussed.

2. In all the cases, except 7, the treatment was conservative, without decompression.

3. Seven patients with depressed fractures and 3 patients with elevated fractures were treated without operation. All recovered.

4. Lumbar puncture should not be done for diagnosis when diagnosis can readily be made otherwise.

5. Children suffering from fracture of the skull should, in most cases, be treated conservatively.

5412 North Clark Street.

75. Cushing, H. W.: Cranial Hyperostosis Produced by Meningeal Endotheliomas, *Arch. Neurol. & Psychiat.* 8:139 (Aug.) 1922.

TORSION OF THE OMENTUM

ITS CLINICAL IMPORTANCE *

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The great or gastrocolic omentum has never played a particularly prominent part in clinical surgery, its rôle generally being accepted rather as that of an inert structure with a function more or less vague and a relationship to clinical symptoms too remote to merit serious consideration in the diagnosis of abdominal conditions. Of late, however, in consequence of the rapid accumulation of reports and data relative to torsion of the omentum, this structure has assumed some degree of clinical importance, and it is significant of this altered status that at least one modern surgical text¹ has given prominent consideration to this disease in the differential diagnosis of acute appendicitis. Accordingly, the conclusion now seems justified that, under certain conditions, the omentum possesses inherent potentialities capable of initiating abdominal crises which demand differentiation from other and more familiar acute abdominal lesions.

In an abstract physical sense, torsion of a structure may be defined as a turning or twisting about its long axis. Two varieties may be recognized: (1) the unipolar, in which the structure is fixed at one extremity while its distal end swings free in response to any forces acting on it; as an example of this type may be mentioned the plumb line, the weighted end of which is suspended in midair; (2) the bipolar, in which the structure is fixed at two points with the intervening portion left free to twist axially; a handkerchief suspended by two diagonally opposed corners, permitting rotation between, has aptly been suggested by Picquet² as an example of this variety.

Clinically, the most familiar examples of torsion are encountered with ovarian cysts, the testicle and the spleen, in which a comparatively heavy, solid mass attached to a long thin pedicle provides ideal mechanical conditions for an axial twist of the unipolar type. A rare instance of torsion involving the lesser omentum and producing symptoms sug-

* Submitted for publication, Oct. 13, 1930.

* Read in abstract before the New York Celtic Medical Society, Jan. 16, 1930.

1. Lewis: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 7, p. 20.

2. Picquet: Bull. et mém. Soc. anat. de Paris 85:717, 1910.

gestive of perforation of the stomach was recorded by Hartwell,³ while Studebaker⁴ mentioned fifty-three cases of torsion of the appendices epiploicae which gave rise to acute abdominal manifestations.

Owing to its character and environment, torsion arising in the great omentum is somewhat more complex, since both the unipolar and bipolar types of rotation may occur. With the omentum swinging normally free from its attachment to the stomach and colon, its dependent portion is acted on by a variety of forces within and without the peritoneal cavity. Hence any factor, such as cysts, tumors, inflammatory tumefaction or circumscribed fibrosis, which produces a local increase in the density of this dependent portion may contribute toward unipolar torsion. More frequently, however, the well known tendency on the part of the omentum to attach some portion of its free border to another intra-abdominal structure accounts for the second fixed point essential to bipolar torsion and in consequence, this type of torsion preponderates when this organ is concerned.

Marchette was credited by Aimes⁵ with reporting the first case of torsion of the omentum, in 1851, but Oberst,⁶ in 1882, presented the first available record of this condition, which was supplemented by that of Demons⁷ in 1893. These cases were all associated with right inguinal hernia, a fact which seemed to establish this complication as a predisposing factor until Eitel,⁸ in 1899, reported the first case of pure abdominal torsion occurring independent of the presence of hernia.

In 1905, Corner and Pinches⁹ compiled from the literature the reports of fifty-one authentic cases, to which they added three of their own, making a total of fifty-four. From the information thus assembled they contributed the most complete study of this subject made before or subsequent to that year. Analysis of the data obtained from this series indicated that torsion of the omentum is a disease of middle life, 78 per cent of the cases having occurred in persons between the ages of 35 and 55, although the youngest patient was 17 (a case reported by Broca¹⁰) and the oldest, 79 (a case reported by Weiner¹¹). Males were more commonly affected than females, in the proportion of 69.7 to 32 per cent. The importance of inguinal hernia as a predisposing factor was shown by the fact that it was present in 90 per cent of the

3. Hartwell: *Ann. Surg.* **61**:626, 1915.

4. Studebaker: *J. Iowa M. Soc.* **11**:350 (Sept.) 1921.

5. Aimes: *Progrès méd.* **34**:425, 1919.

6. Oberst: *Zentralbl. f. Chir.* **27**:441, 1882.

7. Demons: *Rev. de chir.* **13**:159, 1893.

8. Eitel: *M. Rec.* **55**:715 (May 20) 1899.

9. Corner and Pinches: *Am. J. M. Sc.* **130**:314, 1905.

10. Broca: *Bull. et mém. Soc. de chir. de Paris* **26**:170, 1900.

11. Weiner: *Ann. Surg.* **32**:648, 1900.

cases. Furthermore, these herniae presented certain common features which were regarded as of definite etiologic significance; namely, they were usually in the right inguinal region, scrotal in type, of long duration and easily reducible, and they almost invariably contained omentum.

Six, or 10 per cent, of the cases in this series were of the so-called pure abdominal type; i. e., the torsion developed within the abdomen and was not associated with any type of hernia. The latter group attracted particular interest, not only because of the absence of an associated pathologic process and the obscurity of the mechanism of their production, but also because of the diagnostic difficulties that they created. Interest in this phase of the subject has been sustained to the present time. In 1928, McWhorter,¹² in a study of this type of torsion, collected twenty-four of these cases, to which he added two of his own.

In the early cases, classification was rendered superfluous by reason of the fact that all of them could be included in a single category; namely, the hernial. Subsequent reports, however, brought out, in addition to Eitel's case, instances of pure abdominal, nonhernial torsion together with certain subvarieties of the hernial type itself, thus calling for some form of grouping.

The effort to provide such a grouping competent to cover all the observed types of torsion has resulted in a variety of classifications which are, in many instances, as elaborate and complex as they are numerous. In spite of the fact, however, that they appear to differ in nomenclature and arrangement, all these classifications are essentially identical in their fundamental recognition that all cases of torsion fall into one of two main groups: (*a*) torsion with an associated pathologic process, e. g., hernia, and (*b*) torsion without demonstrable associated disease. No consideration has therefore been given to the conception that torsion may be complete or incomplete, and no attempt has been made to distinguish between the acute and chronic varieties of this condition. It is therefore my purpose to emphasize the clinical import of the latter phases of torsion of the omentum, and, as a basis for my description it is advisable to adopt the following modified classification, which includes them in their conceived relationship to the other forms.

A. Complete torsion

1. Acute torsion with hernia

(*a*) Hernial

(*b*) Hernial and abdominal (combined)

2. Acute torsion without hernia (purely abdominal)

(*a*) Primary or idiopathic (unipolar)

(*b*) Secondary (unipolar and bipolar)

12. McWhorter, G. L.: Torsion of Omentum Without Hernia, Arch. Surg. 16:569 (Feb.) 1928.

B. Incomplete torsion

1. Chronic recurring torsion (unipolar and bipolar)

(a) With hernia

1. Hernial
2. Combined

(b) Without hernia

1. Primary
2. Secondary

Richardson,¹³ in discussing torsion of the omentum, unconsciously but accurately defined the scope of the terms "complete" and "incomplete" as applied to this classification. "True torsion should include," he stated, "only those cases in which twisting of the omentum on itself has caused sufficient obstruction of the circulation to produce evidences of strangulation." According to my conception, *circulatory obstruction* of this degree presupposes organic changes in the tissues, progressing from simple congestion and edema to thrombosis, infarction and gangrene. It may be assumed also that such changes are permanent, and that they lead to symptomatic manifestations which are acute and from which there is no spontaneous retrogression. This form of torsion therefore fulfils, within the meaning of the classification, the conception of the "complete" type, and under it obviously must also be included those lesions which are acute by reason of the pathologic process produced thereby.

But to continue with Richardson's statement: "The matting of the omentum into a mass or ball which, although a part of the pathological process producing torsion, should not, by itself, be included under this term."

According to the classification given the pathologic process thus described accurately pictures the condition for which the term "incomplete torsion" was adopted. In my opinion, this process which is "a part of the pathological process producing torsion" differs only in degree from so-called "true torsion," and its exclusion from this category must be based solely on the assumption that it plays no part, immediate or remote, in the production of symptoms.

On the contrary, it is possible to demonstrate by clinical evidence, to be presented herein, that the omental changes grouped under the term "incomplete torsion" are responsible for distinctive clinical manifestations which justify the inclusion of this group in any comprehensive classification of torsion of the omentum.

The analysis by Corner and Pinches,⁹ of fifty-three cases of torsion of the great omentum occurring prior to 1905, emphasized the possibilities of this condition and served to familiarize its clinical and

13. Richardson, W. W.: Torsion of the Great Omentum, J. A. M. A. **48**:1590 (May 11) 1907.

pathologic characteristics. The ensuing period has been marked by an added keenness in the recognition of the disease and in consequence thereof the interval from 1905 to 1929 has witnessed a rapid accumulation of authentic, accurately observed cases. In view of the fact that the latter cases present significant new data relative to symptomatology and diagnosis, and as no systematic study of these data has been carried out during this period, it appears advisable to supplement the work of Corner and Pinches by an analytic study of the cases reported in the literature from 1905 to 1929 inclusive.

A careful search of the literature of this period revealed a total of 164 cases, 161 of which were sufficiently complete to permit accurate analysis and classification. Including Corner and Pinches' 1905 series, 217 cases of torsion were therefore available for study.

In my 1929 series, 101 (62.7 per cent) were males and 60 (37.2 per cent) were females; in 3 instances the sex was not indicated. The

TABLE 1.—*Age Incidence by Decades of Torsion of the Great Omentum*

Age, Years	Cases, Number	Cases, per Cent
0 to 10.....	3	1.8
10 to 20.....	5	3.1
20 to 30.....	29	18.3
30 to 40.....	43	27.2
40 to 50.....	40	25.3
50 to 60.....	29	18.3
60 to 70.....	8	5.06
70 to 80.....	1	0.63

average age in this series was 45.3 years. The oldest patient (a case reported by Brown¹⁴) was 80 and the youngest (a case reported by Lawrence¹⁵), 3 years of age. Speese¹⁶ recorded a case of torsion in a patient aged 5 years, Coen¹⁷ in one aged 5, Erdmann¹⁸ in one aged 14 and Strauss¹⁹ in one aged 15. Table 1, in which age is tabulated by decades, indicates that the highest incidence of the disease (43, or 27.2 per cent of cases) occurred during the fourth decade.

For purposes of analytic study, the cases of this series have been grouped in accordance with the classification given and it is therefore essential to clarify and define accurately the scope of the terms employed therein.

The term "torsion" itself, as applied to the great omentum, implies the rotation of that structure about its long axis with the resulting

14. Brown: Brit. M. J. **1**:183 (Jan. 30) 1926.

15. Lawrence: South. M. J. **18**:423 (June) 1925.

16. Speese: Internat. Clin. **30**:246, 1920.

17. Coen: Policlinico (sez. chir.) **35**:252 (May) 1928.

19. Strauss: Beitr. z. klin. Chir. **148**:36 (Nov. 23) 1929.

18. Erdmann: Ann. Surg. **88**:423 (June) 1925.

formation of a narrow neck or pedicle somewhere in its continuity. Disregarding for the moment the causative factors involved in this process, it is obvious that subsequent developments in the involved omentum will be governed by the degree and permanence of the circulatory impairment at the site of the twist. Knowing the character, mobility and environment of the great omentum, it is not difficult to accept the fact that temporary twists of this sort occur and recur frequently; but under ordinary circumstances, spontaneous readjustment takes place before extensive damage is accomplished. Nevertheless, these temporary twists are evidenced clinically through the sympathetic nervous system by certain vague, transitory abdominal symptoms, and their tendency to recur is responsible gradually, through vascular changes, for slight local omental thickening of fibrosis—the so-called “omental ball.”

On the other hand, the torsion occasionally assumes a more definite intensity and permanence, spontaneous readjustment fails to occur, and the lesion becomes progressive. The early congestion at the site of the twist is soon succeeded by edema which intensifies the existing vascular obstruction, and the sequence of thrombosis, infarction and gangrene supervenes in the distal segment of twisted omentum.

Thus the degree of vascular obstruction becomes the basis on which one distinguishes primarily two main varieties of torsion, the complete and the incomplete. The complete type is dynamic and acute, with a rapidly progressive pathologic process and symptoms; the incomplete form is static, with chronically recurrent symptoms of an ill defined nature accompanied by rather indefinite pathologic changes of a non-progressive type.

The presence or absence of hernia associated with the torsion becomes the basis on which the cases of complete torsion are further divided under two main subgroups; namely (1) acute torsion with hernia and (2) acute torsion without hernia. The former includes all cases in which (a) the torsion is confined to the hernial sac (the hernial type [fig. 1a and b]); (b) the torsion within the hernia “runs up” the omentum into the abdomen, producing secondary intra-abdominal pedicles and contorted masses (the combined type [fig. 1c and d]), and (c) the contorted mass is completely intra-abdominal, but the presence of a hernial sac, even though empty, is regarded as sufficient evidence of its etiologic relationship. (fig. 1e).

The latter type, acute torsion without hernia, occurs independently of hernia and is purely abdominal, topographically and etiologically. Its subtypes comprise: (1) a unipolar form in which no direct mechanical factor predisposing to torsion can be demonstrated; it therefore is classed as the “primary” or idiopathic type (fig. 1f); (2) unipolar and bipolar varieties in which definitely associated mechanical factors are

responsible for the initial twist—the secondary type (fig. 1*g* and *h*). These factors may be (*a*) a tumor, a cyst or other causes of increased density in the dependent omentum favoring the unipolar type of torsion or (*b*) the adhesion of the omental tip to the parietes or an adjacent intra-abdominal organ, thus providing a second fixed point which makes possible the bipolar type of torsion.

Under the classification of incomplete torsion are grouped the chronic recurring varieties, but owing to the fact that experience with this type

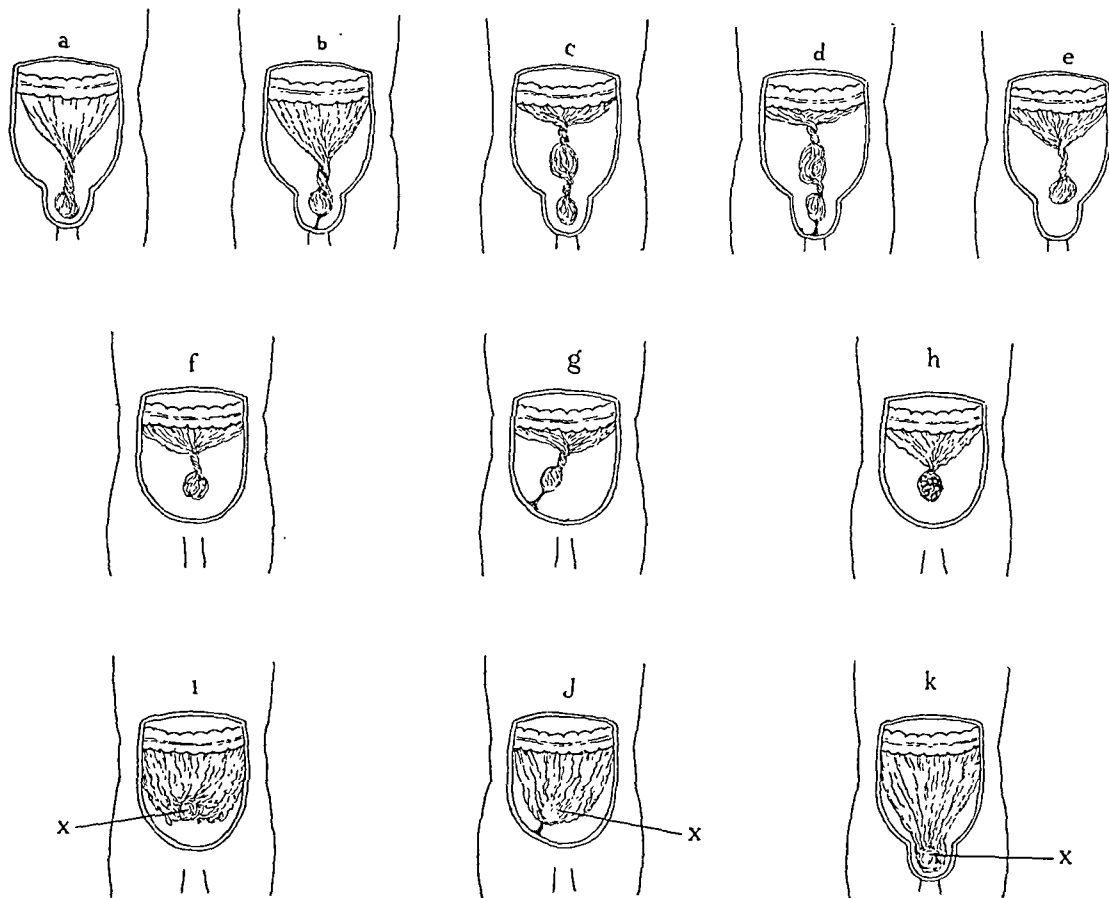


Fig. 1.—*A*, various types of torsion of the omentum: *a*, acute hernial, unipolar; *b*, acute hernial, bipolar; *c*, acute combined, unipolar; *d*, acute combined, bipolar; *e*, acute combined (sac empty); *B*, types of complete torsion without hernia: *f*, acute primary, unipolar; *g*, acute secondary, bipolar; *h*, acute secondary, due to tumor or cyst; *C*, types of incomplete torsion with and without hernia: *i*, primary abdominal (*x*, omental ball); *j*, secondary abdominal, and *k*, hernial.

of case has been comparatively limited, the subvarieties are not so well defined as those of complete torsion. There are discernible, however, certain similar anatomic and mechanical factors common to both the complete and the incomplete types of torsion, thus suggesting that analogous subtypes should occur under each of them. In order, therefore, to carry the present classification to completion and so anticipate

the results of further observation, this analogy has been drawn on for the purpose of achieving a satisfactory terminology for the subtypes under incomplete torsion.

ANALYSIS OF THE CASES

Of the total of 164 cases in the 1929 series, 161 showed the complete type of torsion. Of these, 81 (50.3 per cent) were associated with hernia, while 77 (47.8 per cent) were of the purely abdominal or nonhernial type. When these figures are compared with those of Corner and Pinches' 1905 series in which 11 per cent (compared with 47.8 per cent) were purely abdominal and 89 per cent (compared with 50.3 per cent) were associated with hernia, it is evident that the period from 1905 to 1929 has been marked by a striking increase, relative as well as absolute, in the purely abdominal type of case. This increase, however, is obviously more apparent than real and is to be interpreted as the result of a combination of factors: 1. The impression gained from the early cases, that hernia was an essential etiologic accompaniment of torsion, was dispelled, in the light of wider experience, to permit the inclusion of many cases of pure abdominal torsion previously overlooked. 2. The increasing popularity and efficiency of the radical surgical treatment for inguinal hernia was unquestionably responsible for the elimination of potential sources of hernial torsion in many instances. 3. The substitution of surgical methods of treatment for the older method of taxis, which of itself accounted for numerous cases of torsion with hernia, further reduced the incidence of this type.

ACUTE TORSION WITH HERNIA

Under the heading of acute torsion with hernia are placed eighty-one (50.3 per cent) of the cases of the series, and within this group two subvarieties are to be distinguished: (1) the intrasacular, comprising 16 (19 per cent) of the group, in which the torsion was limited to the hernial sac (fig. 1), and (2) the combined, numbering sixty-five (80 per cent) of the group in which (*a*) the torsion was not limited to the hernial sac but extended upward to produce secondary masses and pedicles in the abdominal portion of the omentum (fig. 1), or (*b*) the contorted omental mass was found entirely within the abdomen but an accompanying hernial sac, although empty, was accepted as evidence of the hernial origin of the torsion. Nevertheless, Smythe,²⁰ Hedley,²¹ and Mesa,²² in reporting cases of this type, emphasized that "the torsion had no connection with the hernia," thus evidently implying a primary

20. Smythe: *Surg., Gynec. & Obst.* **3**:531, 1906.

21. Hedley: *Brit. M. J.* **2**:1246, 1911.

22. Mesa: *Semana méd.* **30**:949, 1923.

abdominal origin of the torsion and eliminating the hernia as an etiologic factor. It is, however, clear from clinical experience with the hernial types of torsion that spontaneous reduction of the hernial mass of omentum occurs with considerable frequency, and that the torsion is thereupon found to be entirely intra-abdominal, the sac is empty, and no evident anatomic connection exists between the two parts. The existence of a hernia in conjunction with an intra-abdominal torsion is therefore accepted as establishing the hernial nature of the latter, and the demonstration of an actual anatomic connection is not essential to its classification under the combined form of torsion.

Among the herniae associated with acute hernial torsion are found representatives of all the external abdominal varieties. Their types and their distribution in the series are indicated in table 2.

Therefore, of eighty-one cases of acute hernial torsion, the accompanying hernia was inguinal in 93.7 per cent, umbilical in 24 per cent,

TABLE 2.—*Types and Distribution of the Accompanying Herniae in Acute Hernial Torsion*

Type of Torsion	Inguinal Hernia, Right	Inguinal Hernia, Left	Umbilical Hernia	Ventral Hernia	Femoral Hernia, Right
Intrasacular.....	8	5	2	1	0
Combined.....	58	5	0	1	1
Total.....	66	10	2	2	1
Percentage.....	(81.4)	(12.3)	(2.4)	(2.4)	(1.2)

ventral in 2.4 per cent and femoral in 1.2 per cent. Of those herniae which occurred bilaterally; namely, inguinal and femoral, the right side was implicated in 87 per cent and the left side in 13 per cent.

The duration of the hernia is of some interest from an etiologic standpoint. It was referred to in forty-seven of the histories in this group. In thirty-one of these, the average duration was seventeen years, the shortest being two and the longest being forty years; while in the remaining sixteen cases this period was described as "long standing," "since childhood," "many years." etc. In seven of the cases, torsion developed in association with herniae which had recurred after operation. In the cases of Bufalino²³ and Cavara²⁴ the herniae had recurred after the second operation, the torsion being related to the second hernial recurrence. In Reidel's²⁵ case, torsion occurred in conjunction with a hernia which recurred after treatment by means of a truss. Grant²⁶ cited an instance in which torsion was observed at the site of a hernia apparently cured by the use of a truss two years previously.

23. Bufalino: Policlinico (sez. chir.) **31**:289 (June) 1924.

24. Cavara: Semana méd. **1**:223 (Jan. 24) 1929.

25. Reidel: München. med. Wchnschr. **52**:2257 (Nov. 21) 1905.

26. Grant: Colorado M. J. **5**:195, 1908.

In addition to their long duration, these herniae, particularly the inguinal type, disclosed other common characteristics that may have a distinct bearing on the production of omental torsion. They were usually of the well developed scrotal type, easily reducible and, as a rule, giving rise to no pain up to the onset of the acute attack. The contents of the sac were almost invariably omentum, and reduction had been practiced habitually by the patient or the attending physician over a period of years.

The stature or make-up of the patient was referred to in twenty-four of the cases; in twenty-one of these, the patient was described as "obese," "fat" or "robust," while only three were classed as "thin." The preponderance of the obese type in this small group scarcely justifies the conclusion that obesity is a characteristic of the patient with torsion, but it is probable that more careful observations would have established that the majority of these persons are well nourished. This consideration is of some etiologic importance and will be referred to again under that heading.

The onset of the immediate attack was described as acute in forty cases and subacute in ten; in thirty-one of these the onset was attributed to a definite exciting cause. In ten instances²⁷ the attack began during or shortly after lifting a heavy object or followed extreme muscular strain. Heavy falls initiated the symptoms in four cases,²⁸ sharp blows on the abdomen were described as causative in seven cases,²⁹ and in three cases the attack followed the forcible reduction of a scrotal hernia.³⁰ In Verbely's³¹ case the attack occurred while the patient was bowling, in Schönwerth's³² case while the patient was stretching across a table and in Thevenard's³³ case during the course of a bicycle ride. Patel and

27. McWhorter (footnote 12). Reidel (footnote 25). Kohler: *Arch. f. klin. Chir.* **3**:514, 1918. Mullen: *Surg., Gynec. & Obst.* **40**:635 (May) 1925. Siefert: quoted by Mast: *Med. Welt.* **2**:128, 1928. Nixon: *Texas State J. Med.* **20**:659 (April) 1925. Lapeyre: *Bull. et mém. Soc. de chir. de Paris* **33**:192, 1907. Lucene and Mondor: *Bull. Soc. anat. de Paris* **6**:346, 1911. Allen: *J. Iowa M. Soc.* **14**:549 (Dec.) 1924. Wildenskov: *Ugesk. f. læger* **82**:40, 1920.

28. Tuffier: *Bull. et mém. Soc. de chir. de Paris* **32**:301, 1906. Uffreduzzi: *Gior. d. r. Accad. di med. di Torino* **18**:45 and 106, 1912. Syme: *Intercolon. M. J. Australasia*, 1902, p. 444. Hedley (footnote 21).

29. Studebaker (footnote 4). Eitel (footnote 8). McWhorter (footnote 12). Bazy, quoted by Aimes (footnote 5). Cernezzi: *Clin. chir.* **17**:664, 1909. Lucene and Mondor (footnote 27, eighth reference). Hadda: *Arch. f. klin. Chir.* **92**:843, 1910.

30. Arcoleo: Morgagni, 1909, p. 422. Hotchkiss: *Ann. Surg.* **45**:759, 1907. Albrecht: *Gynäk. Rundschau* **5**:259, 1911.

31. Verbely: *Wien. med. Presse* **48**:1561, 1907.

32. Schönwerth: *Beitr. z. klin. Chir.* **48**:118, 1906.

33. Thevenard: *Paris chir.* **3**:38, 1911.

Santy,³⁴ Morestin³⁵ and Taddei³⁶ reported cases in which drastic catharsis seemed to initiate the trouble. In Pretzsch's³⁷ case, symptoms developed while the patient was dancing.

Whether ushered in in this manner or, as frequently occurred, developing independent of a demonstrable exciting cause, the onset of the acute attack was usually first expressed as a change in the character of the hernia which, having previously been easily reducible and painless, was suddenly observed to be irreducible, tender, firm and sometimes increased in size. The pain that accompanied these changes was, in a few instances (intrasacular types), confined to the scrotum; as a rule, however, it was first manifested generally over the abdomen before eventually localizing to the right, of the umbilicus or in the right lower quadrant (combined types). This pain was usually of a severe, colicky, prostrating type, which "doubled up" its victims and at times gave the impression of an acutely perforated viscus. Nausea and vomiting followed in 45 per cent of the cases, elevation of temperature (from 99 to 102 F.) in 58 per cent and acceleration of pulse in 26 per cent. In twelve cases in which blood counts were recorded there was a leukocytosis ranging from 12,000 to 19,000 white blood cells. Tenderness was almost invariably elicited to the right of the umbilicus and in the right lower quadrant of the abdomen. Spasm of the right rectus muscle was a frequent observation, usually preventing accurate palpation of the structures beneath. In twenty of the cases, however, a large firm, tender mass could be felt in the right lower quadrant of the abdomen soon after the onset of the attack. In a large proportion of these cases the mass was freely movable. Mesa's²² patient was able to secure relief from pain by displacing the tumor upward by means of external pressure. In two cases³⁸ the discovery of the mass per vaginam led to a diagnosis of twisted ovarian cyst. In isolated instances, inconstant symptoms, such as dysuria, diarrhea and jaundice, were observed during acute attacks; in one case, bleeding from the stomach was noted by Gillette,³⁹ while Wildenskov's⁴⁰ patient experienced intestinal hemorrhages.

The gross pathologic process encountered in conjunction with these clinical manifestations was essentially similar throughout the group of cases of torsion with hernia, although considerable variation in the degree and extent of the process was described.

34. Patel and Santy: *Lyon chir.* **10**:35, 1913.

35. Morestin: *Bull. Soc. anat. de Paris* **89**:85, 1914.

36. Taddei: *Riforma med.* **37**:289 (March 26) 1921.

37. Pretzsch: *Beitr. z. klin. Chir.* **48**:118, 1906.

38. Tuffier (footnote 28, first reference). *Cinaglia: Gazz. d. osp.* **34**:859, 1913.

39. Gillette: *Am. J. Obst.* **63**:112, 1911.

40. Wildenskov (footnote 27, tenth reference).

Typical of the intrasacular variety was a long thin pedicle with a variable number of twists occupying the inguinal canal and often reaching as high as the internal ring. This pedicle communicated in the distal hernial sac with the thickened congested or gangrenous mass of omentum which was sometimes adherent at one or more points in the sac (bipolar), but was as frequently found free therein with no second fixed point present (unipolar).

In the more common combined variety, the twisting process "ran up" through the inguinal pedicle to produce secondary masses and pedicles in the abdominal portion of the omentum. In some extreme cases this progressive twisting process resulted in a series of two or three intra-abdominal masses with intervening pedicles, and sometimes involved the entire omentum up to its origin at the transverse colon. More characteristic of this combined type, however, was the single intra-abdominal omental mass usually situated in the right lower quadrant or the right umbilical region. Proximally, it presented a twisted pedicle extending up the omentum for a variable distance, while distally it communicated with the scrotal mass by way of the inguinal pedicle.

An important and significant characteristic of combined torsion is the freedom of the inguinal pedicle in its course through the inguinal canal and the internal ring. This feature emphasizes the fact that the circulatory changes distal to this pedicle are due to its intrinsic twisting mechanism rather than to the constricting effect of the contiguous parts of the canal. On the other hand, strangulated omental herniae, which at operation may closely resemble scrotal torsion in most other respects, present definite evidence of constriction at the internal ring or within the canal to account for the distal vascular changes.

Differentiation between these two conditions is of more than academic interest. Demons⁷ operated on an apparently uncomplicated strangulated omental hernia and removed a gangrenous omental mass the pedicle of which was amputated at the internal ring. The persistence of abdominal symptoms led subsequently to laparotomy, which disclosed a peritonitis secondary to the gangrenous intra-abdominal portion of a previously unrecognized combined torsion of the omentum. Trinkler⁴¹ operated in a similar case, but recognizing the significance of a free, nonconstricted pedicle, he extended his incision and removed an intra-abdominal mass of twisted omentum.

It is therefore evident that the finding of a supposed omental hernia, the scrotal mass of which presents evidence of vascular obstruction combined with a free, nonconstricted inguinal pedicle, should arouse

41. Trinkler: *Deutsche Ztschr. f. Chir.* 75:269, 1904.

suspicion of combined torsion with the possibility of an associated intra-abdominal pathologic process.

The gross structural changes encountered in the omental masses thus produced varied with the degree of circulatory obstruction produced at the site of the twist, but were not necessarily proportional to the number of twists present. In many instances, these changes had not proceeded beyond the stage of thickening, fibrosis and "omental ball" formation, the normal color and lobulation of the omentum being preserved. In others, in which circulatory obstruction was more definite, edema, congestion thrombosis, infarction and even gangrene had developed, the normal lobular structure was lost and the mass assumed a beefy consistency with a color varying from red to violet or black.

These omental changes were usually responsible for, and accompanied by, evidences of reaction on the part of the peritoneum to the presence of the intra-abdominal mass. The nature of this reaction was determined by the severity of the omental process. In many instances numerous fine adhesions between the mass and such contiguous structures as the abdominal wall, intestine or uterus betokened a low grade inflammatory irritation. The filmy character of these adhesions indicated a recent formation and distinguished them definitely from the more dense, permanent omental adhesion which was often coexistent as the "second fixed point" in the bipolar type of torsion. In the more acutely involved cases free fluid was a common observation; in twenty-five (30 per cent) of the cases, considerable quantities of this fluid, serosanguineous to frankly bloody, was described as a prominent feature at laparotomy.

From the data thus accumulated, a composite clinical picture of a hypothetical case of torsion with hernia may be constructed. The patient is usually an obese, robust or well nourished man in middle life who for years has had hernia, most probably of the right inguinoscrotal type. During this period the hernia has not caused pain and has been easily reducible. Suddenly, and often following a severe physical strain or muscular effort, it becomes irreducible, painful and increased in size. The pain becomes severe, colicky or prostrating, and gradually extends up over the abdomen to localize to the right of the umbilicus or in the right lower quadrant. During the next twenty-four to forty-eight hours, the patient's condition becomes progressively worse, with a rising temperature, nausea, vomiting and an accelerated pulse rate. Abdominal examination discloses tenderness and rigidity on the right side. A large, tender, movable mass suddenly makes its appearance in the right lower quadrant. Blood counts show a moderate leukocytosis.

The preoperative diagnosis usually rests between acute appendicitis with abscess and a strangulated inguinal hernia. If the latter is made,

herniotomy exposes in the hernial sac a congested or gangrenous mass of omentum, the omental pedicle of which extends upward to the internal ring. This pedicle may present evidence of twisting, but of even greater significance is the absence of any point of constriction within the canal or at its internal ring to account for the circulatory changes below. It is this combination of a free pedicle with distal circulatory disturbances which suggests the possibility of intra-abdominal extension of the torsion (combined type). Recognition of the importance of these relations will lead, in a certain percentage of cases, to herniolaparotomy with indications characteristic of the combined type of torsion.

ACUTE TORSION WITHOUT HERNIA

In seventy-seven (47.8 per cent) of the cases in the series, torsion occurred independent of the presence of hernia and was therefore purely abdominal in location. Within this group the cases were divided into two subtypes: (1) the primary or idiopathic and (2) the secondary. Forty-one (53.2 per cent) of the cases were included under the heading of primary torsion because they appeared to be of spontaneous or idiopathic origin; i.e., there was no evidence of an antecedent change in the omentum or in its environment to account for the initiation of the twisting process. On the other hand, thirty-six (46.7 per cent) of the cases of this group presented definite evidence of preexisting pathologic factors which were mechanically competent to precipitate a torsion and they were accordingly classed as the secondary type. These factors were of three distinct types: (*a*) inflammatory processes in structures adjacent to the omentum; in thirteen of the thirty-six cases of secondary torsion, the appendix showed evidence of acute, subsiding or comparatively recent inflammation (the significance of this fact will be further touched on under etiology); (*b*) tumor, cyst or other areas of increased density in the free, dependent portion of the omentum. The relation of this condition to torsion was discussed under mechanics of unipolar torsion, and three cases illustrative of this type were included in this series; in Tuffier's case, a hydatid cyst of the omentum was apparently responsible for the inception of the twist; Speese reported a case in a child aged 5 years, and Lawrence a case in a child aged 3, in both of whom an omental cyst of congenital origin appeared to be the inciting stimulus to an acute torsion; (*c*) adhesion of a portion of the free margin of the omentum to some adjacent structure. As pointed out under bipolar torsion, there is thus established the second fixed point which forms, with the normal fixed point of the omentum at its origin, an axis about which the adjacent portions of the omentum tend to rotate. In nineteen of the thirty-six cases of the secondary type, torsion had occurred between two such fixed points and was therefore of the bipolar

variety. Various intra-abdominal structures shared with the omentum in the formation of this "second fixed point." In five cases the distal omental adhesion was at the stomach, ascending colon or cecum; in four cases the point of fixation was somewhere on the anterior abdominal wall; in three cases an omental tongue had attached itself to an ovarian cyst which had itself undergone torsion, the omental torsion evidently being a secondary process.⁴² In the pelvis, the uterus—pregnant in one instance—served as the "second fixed point" in three cases while in three other cases an inflamed right tube was responsible. Luckett⁴³ operated on a patient in whom a tongue of omentum, tied off with the sac during a previous operation for inguinal hernia, had become the "second fixed point" of a bipolar torsion.

The gross omental changes encountered in the intra-abdominal types of torsion were, in principle, similar to those described under the heading of torsion with hernia. In general, however, the damage to the tissues was more extensive in the former, in which red infarction was frequent and actual gangrene not uncommon. The unipolar types presented the largest masses, as a rule, and in a considerable proportion the entire omentum was involved up to a short thin pedicle at the transverse colon (case 1). In the bipolar varieties the pedicles tended toward greater length and were occasionally double, and the masses were much smaller (case 2). Peritoneal irritation was evidenced, as in the hernial cases, by fresh filmy adhesions between the mass and surrounding structures, while large quantities of free fluid were usually found when the peritoneal cavity was opened.

It is of interest to note that in all of the aforementioned types of secondary torsion the omental mass was almost invariably located to the right of the midline and usually in the right lower abdominal quadrant. The same tendency toward localization on the right side was observed in the hernial cases and was accounted for by the predominance of right inguinal hernia over all other types. In the nonhernial group, however, it is evident that hernia no longer plays a part and that another explanation for this rather constant right-sided localization must be sought. Two factors suggest themselves: 1. It is a matter of common clinical experience that the right margin of the omentum is the more mobile, that it usually hangs well down on the right side and that the left margin is commonly found curled up in the left hypochondrium. It is therefore obvious that the right side presents conditions which favor

42. Potherat: Bull. et mém. Soc. de chir. de Paris **34**:922, 1908. Frederick: Am. J. Obst **56**:742, 1907. Payr: Arch. f. klin. Chir. **68**:501, 1902.

43. Luckett, W. H.: Torsion of the Greater or Gastrocolic Omentum, J. A. M. A. **54**:1364 (April 23) 1910.

torsion of the unipolar variety. 2. The right side, and particularly the right lower quadrant, of the abdomen is a fertile field for the development of acute and chronic inflammatory processes: cholecystitis, gastric and duodenal ulcer and especially appendicitis. These conditions lead frequently to inflammatory fixation of a portion of the free margin of the adjacent omentum (second fixed point) in this region and thus predispose toward the bipolar type of torsion.

The clinical manifestations of the nonhernial type of torsion paralleled closely those of the hernial type, with the single exception that the former, in the absence of associated hernia, presented symptoms confined to the abdomen. Among the predisposing clinical evidences, the stature or make-up of the patient appeared to have a more definite bearing than in the hernial group. In thirty-four (44 per cent) of the cases of the former group, this feature was referred to, and in thirty-one the patient was classed as "obese," "stout" or "well nourished." Only three patients were described as "thin." In twenty-seven cases (35 per cent) the past histories disclosed evidence of vague intermittent digestive disturbances extending over a period of months or years which, in the light of final developments, could be interpreted as of omental origin. As already shown, in thirty-one cases the onset of the acute attack was related to a definite exciting cause: Ten cases followed heavy lifting or severe muscular effort, seven occurred after blows on the abdomen, while in four cases the onset was variously attributed to horseback riding,⁴⁴ violent coughing,⁴⁵ stooping over a tub⁴⁶ and being violently whirled about while wrestling.⁴⁷ The immediate attack was acute and severe in onset in 55 cases (71 per cent) and subacute in twenty-two (28 per cent). Characteristic symptoms accompanying the attack were nausea and vomiting, (42 per cent) elevation of temperature (70 per cent), leukocytosis (44 per cent) and acceleration of the pulse rate (41 per cent). Muscular rigidity and tenderness were constantly found to the right of the umbilicus or in the right lower quadrant. In thirty cases (38 per cent) a definite intra-abdominal mass was palpated soon after the onset of the attack, and the fact that a diagnosis of acute appendicitis or abscess of the appendix was made preoperatively in forty-nine cases (63 per cent) is indicative of the character and location of this mass.

The clinical and pathologic characteristics of acute torsion without hernia are well exemplified by the following two cases. Both belong to the secondary group of torsion. Case 1 represents a unipolar torsion

44. Ill: *Am. J. Obst.* **56**:742, 1907.

45. Adler: *Arch. f. klin. Chir.* **83**:250, 1907.

46. Ronald: *Brit. M. J.* **1**:811 (May 4) 1929.

47. Cullen: *Bull. Johns Hopkins Hosp.* **16**:401, 1905.

associated with an inflammatory process outside the omentum and case 2 illustrates the effects of the "second fixed point" in its relation to bipolar torsion.

REPORT OF CASES

CASE 1.—C. K.,⁴⁸ a white man, aged 28, a clerk, was admitted to the Post-graduate Hospital on Jan. 28, 1926, in an acute condition. Two days previously, he had suddenly been seized with severe generalized abdominal pain accompanied at the onset by nausea and vomiting. Within the following twelve hours the pain, undiminished in severity, localized in the right lower quadrant, and there remained continuous up to the time of admission to the hospital; it did not radiate. There was no dysuria, polyuria or diarrhea, and no history of trauma or muscular strain was obtained.



Fig. 2.—Specimen removed from patient in case 1, showing pedicle (*P*), partially untwisted, and gangrenous mass of omentum.

The previous history was unimportant. He had never experienced an attack similar to the present one, had never noted any form of digestive disturbance, and had never suffered from any type of acute or chronic illness.

The patient was short, thick-set and obese, weighing over 200 pounds (90 Kg.). On his admission to the hospital, his rectal temperature was 102 F. and his pulse rate 110. The abdomen was tympanitic throughout, while generalized tenderness and rigidity precluded the possibility of detecting an intra-abdominal mass. Both rigidity and tenderness seemed more marked over McBurney's point. The presence of free fluid could not be demonstrated by percussion and palpation. Urinalysis yielded negative results. A blood count showed 16,600 white blood cells with 83 per cent polymorphonuclears and 17 per cent lymphocytes. The preoperative diagnosis was ruptured appendix with general peritonitis.

Operation.—A right rectus muscle splitting incision was made. When the peritoneum was opened, a considerable amount of thin serosanguineous fluid escaped. Immediately beneath the incision a large, firm, brownish-red mass pre-

48. This patient was presented before the Surgical Section, New York Academy of Medicine, on May 7, 1926.

sented and seemed to fill the entire right side of the abdomen. On exploration this mass proved to be made up of the entire great omentum, which was twisted on itself just below the right half of the transverse colon where the twisted portion was gathered into a narrow pedicle with seven turns. Distal to this pedicle was the large, firm, beef-red mass representing the entire great omentum. The appendix was acutely inflamed, but was not involved in the omental mass. The omental pedicle was tied off, and the mass was removed. The appendix was then removed in the usual manner, and the abdomen was closed without drainage. Convalescence was uncomplicated, and the patient subsequently enjoyed perfect health.

The pathologic report was: subsiding acute appendicitis and hemorrhagic infarction of the great omentum.

CASE 2.—M. O., a white man, aged 38, a clerk, was admitted to the fourth surgical division, Bellevue Hospital, on Feb. 9, 1928. He had enjoyed excellent health until the day before admission, when he first noted a dull pain in the right lower abdominal quadrant. He was able to continue his work and take food without distress, but the pain grew steadily worse during the day. On going to bed that night, he found that he could not lie on the affected side without great discomfort. At no time was there any associated nausea, vomiting, diarrhea or urinary disturbance. No history of trauma or physical strain was obtained. The bowels had been regular up to the onset of the present attack. During the night the pain became so severe that the patient decided to enter the hospital.

Examination disclosed an unusually robust white man whose weight was estimated at about 200 pounds. General physical observations were entirely negative, except for the protuberant obese abdomen which was distended and tympanitic. The right rectus muscle presented some spasm, and there was definite tenderness localized in the region of McBurney's point. There was a suggestion of a mass in this region, but the muscular spasm and obesity rendered this uncertain. The rectal temperature on the patient's admission was 101 F.; urinalysis yielded negative results; the white blood cells numbered 11,600, with 70 per cent polymorphonuclears. The preoperative diagnosis was acute appendicitis.

Operation.—A right rectus muscle splitting incision was made. A small amount of thin, bloody fluid was evacuated on opening the peritoneum. Just beneath the incision, a narrow tongue of omentum was found extending downward and outward to the right to become adherent to the anterior abdominal wall in the region of McBurney's point. Near its distal end a twist had taken place, shutting off a tab the size of a walnut, which was black and gangrenous. The appendix and gallbladder were normal in appearance. The mass was separated from the abdominal wall, and the tongue of omentum was tied off and amputated at its origin. The abdomen was closed without drainage. Recovery was uneventful, and the patient remained free from symptoms.

Pathologic examination revealed a mass, 3 by 2 by 1 cm., which resembled thyroid tissue. A section showed fat tissue infiltrated by hemorrhage.

Comment.—Cases 1 and 2 are typical examples of two varieties of secondary torsion. Case 1 belongs to the unipolar type referred to under group *a* as associated with an extra-omental inflammatory focus—in this instance acute appendicitis. It illustrates well the tendency of this type of unipolar torsion to form large masses with thin, tight pedicles and a well advanced stage of circulatory impairment. In this

instance the mass filled the entire right side of the abdomen and measured 12 by 5 by 3 inches (30 by 12 by 7 cm.) (fig. 2). The history, course, physical and laboratory observations simulated the classic picture of acute appendicitis so accurately that a differential diagnosis could not be made preoperatively.

Case 2 belongs to the bipolar variety of torsion referred to under group *c*. Adhesion of the free margin of an omental process to the anterior abdominal wall provided the "second fixed point," and rotation had taken place between this point and the normal fixed point at the origin of the omental tongue. In this type of torsion the mass is characteristically small, and there may be two or more such masses with intervening pedicles. The symptoms suggested a diagnosis of appendicitis, but in this instance the picture was not as characteristic as that in case 1, and might well have been questioned. Both these patients had the stature that is so frequently associated with torsion of the omentum that its etiologic significance must be given some consideration, namely obesity, an excessive deposit of subcutaneous fat and a lax, protuberant abdomen. In both instances the patient had led a sedentary life, there was no history of abdominal trauma or physical strain, and there was no evidence of previous similar attacks.

CHRONIC RECURRING TORSION

In discussing the foregoing classification, the suggestion was made, purely on theoretical grounds, that temporary twists of the great omentum occur fairly frequently, owing to its character and surroundings. It was assumed that such twists were incomplete in the sense that they did not produce permanent circulatory impairment, but that they were expressed clinically by certain vague abdominal symptoms. It was further shown, in analyzing the histories of the various types of acute torsion, that in a definite percentage of these cases the immediate acute attack of torsion (complete) had been preceded, over considerable periods of time, by intermittent subacute manifestations of a type conceived of as incomplete in origin.

In their consideration of omental torsion, Corner and Pinches⁹ were impressed by the significance of these antecedent subacute disturbances, and in the conclusion of their discussion they stated:

These (the previous attacks) may be produced by colic, appendicitis or some such condition quite unconnected with omental twists. But many twists—sometimes 10—are frequently found. These have been formed by slow increments of the torsion. It is tempting and not irrational to refer the previous attacks of pain to some of the increments being greater or more forcible than the others. This is borne out with regard to the testis; for instance, the more acute increase in torsion which caused the attack of pain has been untwisted giving perfect relief. Future observers will gain much in paying more attention to the history

of cases of this nature. If this surmise is correct, that these attacks or some of them are produced by increased twists although only the more severe cases are yet recognized, the previous history of the patients illustrates the clinical history of milder examples due to subacute and chronic torsion of the omentum and hitherto unrecognized. It may be expected confidently that the observations in the future will tend to make occurrence of omental torsion more frequent just as in cases of torsion of the bowel and of the testis.

The clinical effects of this type of temporary torsion are seen in structures other than the omentum in which a comparatively large, dense body is suspended by a long, thin pedicle; for example, it is a matter of common clinical experience that temporary incomplete twists of the pedicle of an ovarian cyst may give rise to repeated transitory abdominal attacks the nature of which is unrecognized until the final decisive complete attack leads to operation and discloses the source of the preceding symptoms. I recently saw a premature infant 7 months of age, in whom a swelling in the right groin and scrotum had suddenly developed. For several weeks previous to this occurrence, the patient had had frequent attacks of colic; as there was no associated gastric or intestinal disturbance, the attending pediatrician was at a loss to account for these attacks. At operation, carried out under the diagnosis of strangulated hernia, it was found that a torsion of the right spermatic cord existed and that gangrenous changes in the testicle required its removal. In the light of the observations at operation, it seems logical to refer the antecedent attacks of colic to transitory, incomplete twists of the spermatic cord which had spontaneously untwisted themselves before complete circulatory obstruction supervened.

From the foregoing considerations, certain facts may be assembled in support of the contention that transitory incomplete twists occur in the omentum, and that such twists are responsible for obscure recurrent abdominal symptoms the nature of which usually is unrecognized: 1. It is well known that transitory twists of this type occur in structures other than the omentum (ovarian cysts, testicle) and give rise to similar recurrent abdominal attacks. 2. Physical factors analogous to those favoring torsion in these structures can be demonstrated in the omentum. 3. In a considerable percentage of the cases of acute torsion in this series, there is evidence that the final acute attack was antedated by repeated transitory abdominal disturbances, which may be interpreted as due to incomplete omental twists.

This conception of the omentum as a source of obscure, recurrent abdominal symptoms opens up interesting clinical possibilities, and the inclusion of these conditions under the separate group of incomplete torsion represents an effort to emphasize these possibilities as well as to distinguish them from the acute complete types of torsion.

Abdominal diagnosis is far from precise in spite of the development of exact methods of investigation. Everyday clinical experience is rich in instances of obscure abdominal disturbances the character of which cannot be definitely decided without resort to "exploratory laparotomy" and the frequent failure of this procedure to demonstrate a convincing pathologic process as well as to relieve symptoms is too well known. Undoubtedly, chronic infections of the appendix, gallbladder, stomach and pancreas are factors in many or most of these instances. If it is granted, however, that transitory incomplete twists of the omentum occur, and that these twists are responsible for the clinical manifestations already referred to, it is tempting to attribute to this cause at least a small percentage of these cases.

Systematic examination of the omentum is rarely carried out during the course of exploratory operations, because it is not often thought of as a possible source of trouble. A pathologic process capable of initiating omental twists (e. g., a localized area of fibrosis) may therefore be easily overlooked or its significance may not be appreciated.

The following case illustrates the typical pathologic and clinical features of incomplete torsion of the chronic recurring type:

CASE 3.—G. H., a man, aged 51, a valet, was admitted to the Postgraduate Hospital on Nov. 7, 1929, complaining of pain in the lower part of the abdomen. His present trouble began two months before admission to the hospital, when he began to have periodic attacks of dull pain across the lower part of the abdomen, which was most marked in the suprapubic region. These attacks usually lasted two or three days and were always associated with indigestion and occasionally with vomiting. The movements of the bowels were regular. There was no diarrhea, dysuria or polyuria and no radiation of pain. Between attacks the patient was completely free from symptoms, appetite was normal and there was no indigestion or loss of weight. A large right inguinoscrotal hernia was present but had never given trouble. It had always been reducible and he had never worn a truss. During his most recent attack, he thought that the hernia had increased in size. His previous health had always been good, with the exception of an attack of acute appendicitis in 1926, during which I removed his appendix.

Examination disclosed a large, robust man, well nourished and well developed. General examination gave negative results except that the abdomen was rather protuberant and presented a right paramedian scar. There was a large right scrotal hernia which was painless and easily reducible. It apparently contained intestine. There was no muscular rigidity, and no mass or free fluid could be detected. The temperature and blood count were normal; the blood pressure was 120 systolic and 80 diastolic. The urine showed only a faint trace of albumin.

Operation.—A right inguinal incision was made, and a large, thick inguinoscrotal sac containing only small intestine was delivered. The cord and vessels were dissected free, the sac was opened and the contents reduced. There was no omentum in the sac. The neck of the sac at the internal ring was tremendously dilated and easily permitted abdominal exploration. A large mass of fat-infiltrated omentum was gathered in the right side of the abdomen and hung down into the pelvis, but was not adherent at any point. This mass of omentum was delivered through the internal ring and its redundancy was such that it reached well below the

lower angle of the incision. At the most dependent point of the free margin of the omentum, there was a circumscribed area of thickening and fibrosis forming a mass about the shape and size of a small orange (fig. 3). This thickened area seemed to form the apex of the omental mass, and the lateral margins seemed to drape themselves naturally about the axis thus formed. There was no evidence of active twisting or pedicle formation. The whole mass assumed an elongated ropelike shape at the end of which hung the "omental ball"; the resulting relations might be likened to a handkerchief suspended by one corner and a weight fixed to a diagonally opposite corner while the lateral free corners fall loosely about the central axis. The omentum was drawn down as far as possible, ligated at the highest accessible point and amputated distal to the ligatures. The abdominal cavity could now be easily and thoroughly explored through the enormously dilated

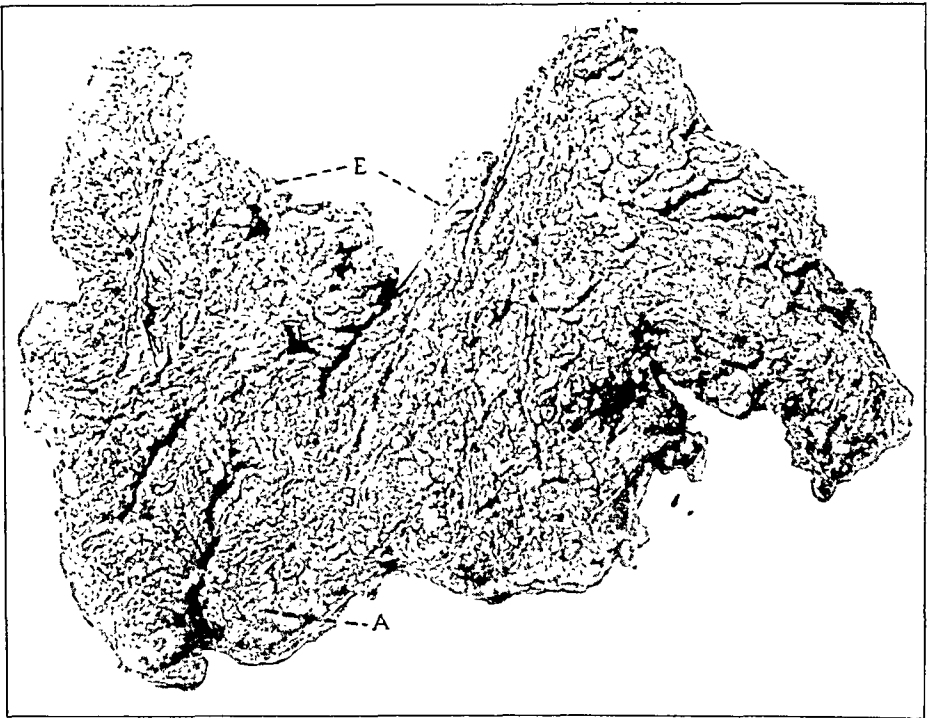


Fig. 3.—Specimen removed from patient in case 3, showing mass of redundant normal omentum with omental ball (*A*) at dependent point. *E* indicates cut edge of omentum.

internal ring. Careful palpation of the stomach, gallbladder, large intestine and pelvis failed to disclose any other pathologic process. The hernial sac was removed, its neck tied off and the canal repaired by the Bassini method.

The patient made a good recovery. When last observed, he had been under constant observation for six months. The abdominal symptoms, which were recurring at weekly intervals previous to operation, had completely disappeared, and the patient was enjoying perfect health.

Comment.—This case is presented as an example of incomplete torsion of the omentum of the chronic recurring type for the following reasons: 1. The pathologic and mechanical conditions found in the omentum favored the development of transitory twists, although

no actual twist or pedicle formation was present at the time of operation. 2. The recurrent abdominal symptoms experienced by the patient were not unlike those reported as preliminary manifestations in a large percentage of the cases of acute torsion in this series, and in latter instances, accepted as evidence of incomplete twists which freed themselves spontaneously. 3. The attacks were completely cured by removal of the offending omentum.

The omental conditions described, i.e., an elongated ropelike structure suspending a comparatively large, dense, tumor mass, seems to provide the mechanical conditions necessary for the development of transitory twists, and it is clear from experience with acute complete torsion that, when such conditions exist, the added stimulus of a blow, a fall or a sudden change of position is all that is required to initiate the twisting process.

There were only two other instances in the series—cases reported by Swain⁴⁹ in 1920—in which the clinical manifestations and associated pathologic process seemed to justify inclusion under the classification of incomplete torsion. The first was in a man, aged 58, with pain in the upper right abdominal quadrant, a palpable mass, tenderness and elevation in temperature. At operation a congested mass of omentum was found near the hepatic flexure, but there was no evidence of a pedicle or twist. The second case was in a woman, aged 25, with vague general abdominal pains which eventually localized about the umbilicus and in the lower right abdominal quadrant, where a palpable tender mass was detected. Operation disclosed a congested mass of omentum without twists or pedicle formation. In both cases the pathologic process was described as “active hyperemia of the omentum,” and the subsequent course in both indicated that the process bore a causative relation to the symptoms produced.

Although the number of clinical instances of incomplete torsion is not impressively large, the available data at least serve the purpose for which this group was primarily introduced into the classification, namely the demonstration of the reality of incomplete omental twists and their potentiality for producing abdominal symptoms. Taking into consideration the evidence presented in case 3, together with that derived from experiences with complete omental torsion and torsion in other structures, I would summarize the salient facts concerning incomplete torsion in the following conclusions:

1. Incomplete twists of the omentum may, under certain conditions, occur and recur intermittently without progressing to the stage of the complete circulatory impairment seen in complete torsion. 2. These incomplete twists are accompanied, as a rule, by recurrent, subacute

49. Swain: *Bristol Med.-Chir. J.* **37**:202 (Dec.) 1920.

abdominal symptoms which, in the light of present clinical experience, are usually attributed to chronic disturbances of the appendix, stomach or gallbladder. 3. The localized areas of omental thickening or fibrosis which characterize incomplete torsion may be readily overlooked during the course of an exploratory laparotomy or, if encountered, their true significance may not be appreciated. It therefore appears probable that incomplete omental twists are responsible for obscure abdominal symptoms more frequently than the foregoing statistics indicate.

DIAGNOSIS

Considering the pathology and clinical picture presented by torsion of the omentum, it is not surprising to find that preoperative diagnosis

TABLE 3.—*Preoperative Diagnosis in 138 Cases of Torsion of the Omentum*

Diagnosis	Torsion With Hernia	Torsion Without Hernia		Incomplete Torsion	Total
		Primary	Secondary		
Acute appendicitis	24	24	16	1	65
Appendiceal abscess	5	3	3	..	11
Appendicitis with peritonitis.....	1	1	2
Appendicitis (subacute)	3	1	..	4
Strangulated inguinal hernia.....	15	15
Inguinal hernia	3	3
Cholecystitis	1	4	3	1	9
Torsion of ovarian cyst.....	3	1	3	..	7
Intestinal obstruction	1	1	1	..	3
Torsion of omentum.....	8	1	1	1	11
Omental hernia	1	1
Tuberculosis of cecum.....	1	1
Strangulated ventral hernia.....	3	3
Torsion of uterine fibroma.....	1	..	1
Torsion of spermatic cord.....	1	1
Pelvic tumor	1	..	1

of this condition has been both varied and inaccurate. Of the entire series of 164 cases, a preoperative diagnosis was recorded in 138. In table 3 is tabulated a list of these diagnoses apportioned to the type of torsion in which they were made.

Analysis of the figures in table 3 brings out points of practical interest; for example, in eighty-two (59 per cent) of the cases, a diagnosis of acute appendicitis or acute appendicitis with abscess or peritonitis was made. This diagnosis was almost twice as common among the pure abdominal types of torsion (torsion without hernia) as in the type associated with hernia (torsion with hernia). Of the nine diagnoses of involvement of the gallbladder, seven were made in the pure abdominal type of torsion, while the twenty-one diagnoses of hernia, strangulated or incarcerated, were made in the hernial type. In only eleven (7.9 per cent) cases was a correct diagnosis of torsion of the omentum recorded and eight (72 per cent) of these showed the hernial type of torsion.

From these figures it appears that torsion of the omentum, whether of the hernial or the purely abdominal type, simulates closely the clinical manifestations of acute appendicitis and, to a lesser degree, of cholecystitis. It is furthermore evident that the associated hernia in the hernial types is an important factor in diagnosis since 72 per cent of the correct diagnoses were made in cases of the latter type, while the diagnosis of acute appendicitis was made twice as frequently in the nonhernial or pure abdominal types.

Smythe²⁰ studied seven cases of pure abdominal torsion in six of which the diagnosis of acute appendicitis had been made; despite these discouraging figures he proposed an elaborate system of differential diagnosis which is summarized briefly in table 4.

TABLE 4.—*Differential Diagnosis of Acute Appendicitis and Torsion of the Omentum (Smythe)*

	Torsion of the Omentum	Acute Appendicitis
Age.....	Usually between 35 and 55	Usually between 15 and 25
Sex.....	Practically all cases in males	Males predominate 6:1
Pain.....	Right lower quadrant in 85%; not sudden or violent	General, then limited to right lower quadrant; may be acute or violent
Pulse.....	Not much affected	Usually accelerated (100 to 140)
Temperature.....	99 to 100 F.	101 to 103 F.
Mass.....	Early, diffuse, large	Second or third day; circum- scribed
Rigidity.....	Not marked	Marked
Percussion.....	Dulness	Resonance
Leukocytosis.....	Usually absent	Usually present
Nausea and vomiting....	Uncommon	Common

In commenting on such a method of differential diagnosis, it is necessary to point out only that it represents an overemphasis on isolated symptoms and that its assumptions, based on a limited number of cases, are not borne out by the symptom analysis of my larger series; for example, it was previously shown that nausea and vomiting, far from being "uncommon" in torsion, occurred as early symptoms in 45 per cent of the cases. Similarly elevation of temperature was present in 58 per cent and acceleration of pulse rate in 26 per cent of this series. It is doubtful if a similar series of cases of acute appendicitis will show any material variation in the incidence of these important diagnostic criteria. So far as the blood picture is concerned, it must be admitted that leukocytosis as an isolated symptom in acute appendicitis is often unreliable and that to place too great dependence on it is to court disaster. Furthermore, this symptom is not "usually absent" in torsion, for the present series discloses white cell counts varying from 12,000

to 19,000 in an appreciable number of cases. Finally, it is self-evident that youth is no bar to torsion or old age to appendicitis.

Clinical symptoms, such as these, can be properly evaluated only when it is recognized that they are nonspecific reactions of a definite physiologic mechanism to varying types of pathology. The symptom of nausea and vomiting, for instance, must be regarded as an expression of reflex sympathetic irritation in which the mechanism and results are identical regardless of the character, but proportional to the intensity, of that irritation. It is therefore to be anticipated that this symptom will occur with approximately equal frequency in both torsion of the omentum and acute appendicitis, provided these lesions are of the same degree of severity. Elevation of temperature, pain, acceleration of pulse rate, etc., obey the same rule and merit the same consideration.

Analysis of the cases in this series has brought out, however, characteristics that may be taken as specific for torsion of the omentum, and that should, in consequence, be helpful in preoperative diagnosis. For example, analysis of the cases has shown that a significantly large percentage of patients with torsion are of a vigorous, robust or obese type whose occupation or environment subjects them to frequent sudden and severe physical strains and abdominal trauma. In the three cases that I observed, the patients were strikingly obese, weighed about 200 pounds (90.7 Kg.) and presented excessive deposits of subcutaneous fat, justifying the recognition of a "torsion habitus." These factors, torsion habitus and physical strain or trauma, are of undoubted importance in the predisposition to torsion of the omentum.

In persons of this type, especially with an antecedent history of repeated attacks of vague, subacute, abdominal symptoms, the acute onset of severe pain in the right lower quadrant of the abdomen, accompanied by the rapid development of a large abdominal mass and free fluid, presents a suggestive picture. The mass itself has certain characteristic features: It is rapid in development, remarkably large, often freely movable and frequently painless. Nausea, vomiting, elevation in temperature, leukocytosis, etc., are merely incidental to a well established peritoneal irritation.

When the hernial types of torsion are concerned, diagnosis is simplified, to a considerable degree, by the presence of the hernia which is always an important clue. This hernia is typically of a long-standing, painless, scrotal variety, the contents of which are almost invariably omentum and have always been easily reducible. When a hernia of this type suddenly changes its character to become irreducible, painful and enlarged and when a large, rapidly developing mass appears simultaneously above Poupart's ligament, acute torsion of the combined hernial type is to be suspected and treated accordingly.



Fig. 4.—Section of omentum from case 1, showing vascular thrombosis, extensive interstitial extravasation and hemorrhage; $\times 60$.

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PATHOLOGY

The gross pathologic changes characteristic of the various types of torsion are well illustrated by cases 1, 2 and 3, and these have already been given in detail. Case 1 is an excellent example of the pure abdominal type of acute torsion without hernia (primary or unipolar variety). The twist had taken place at the transverse colon, and the entire omentum was involved in a firm, beef-red, edematous, congested

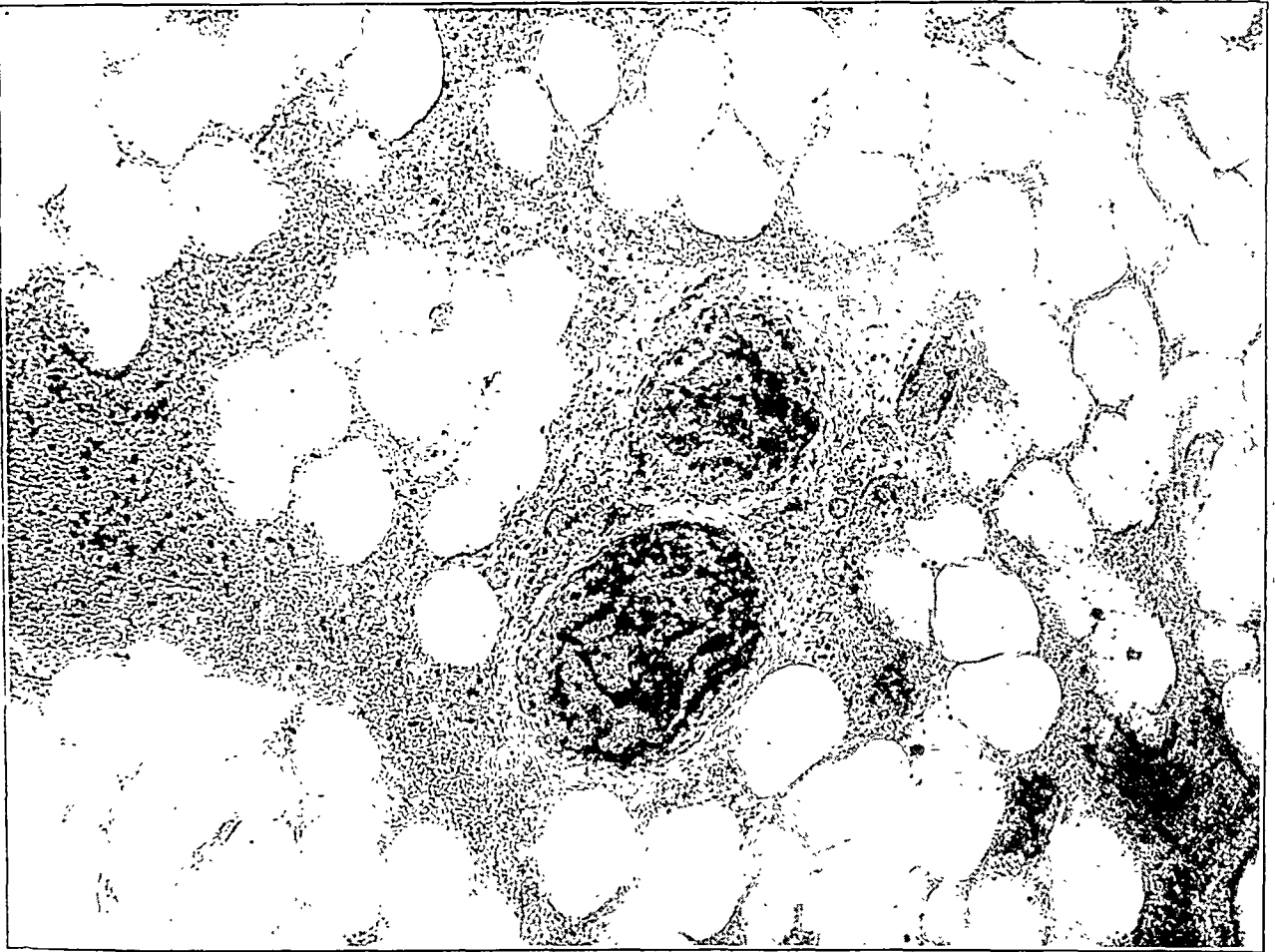


Fig. 5.—Section of omentum from case 2, showing marked thrombosis, hemorrhage and extravasation; reduced from $\times 60$.

mass filling the right side of the abdomen (fig. 2). The microscopic changes observed on section of this mass were disappointing. The smaller and larger vessels showed evidence of stasis and consequent thrombosis, while there was extensive interstitial extravasation of red and white blood cells with areas of actual hemorrhage, particularly marked about the margins of the mass. The actual structural changes were, however, surprisingly limited, and there was little evidence of an inflammatory process or organization (fig. 4). In case 2, an example

of acute intra-abdominal torsion without hernia (secondary or bipolar variety), the mass was small but the hemorrhagic and thrombotic features seemed grossly more pronounced. Yet here also the microscopic details, with the exception of more extensive hemorrhage, were similar to those in case 1 (fig. 5).

Case 3, an example of incomplete torsion, of the chronic recurring variety, presented grossly and microscopically a picture which contrasted markedly with that of complete, acute torsion. The gross omental

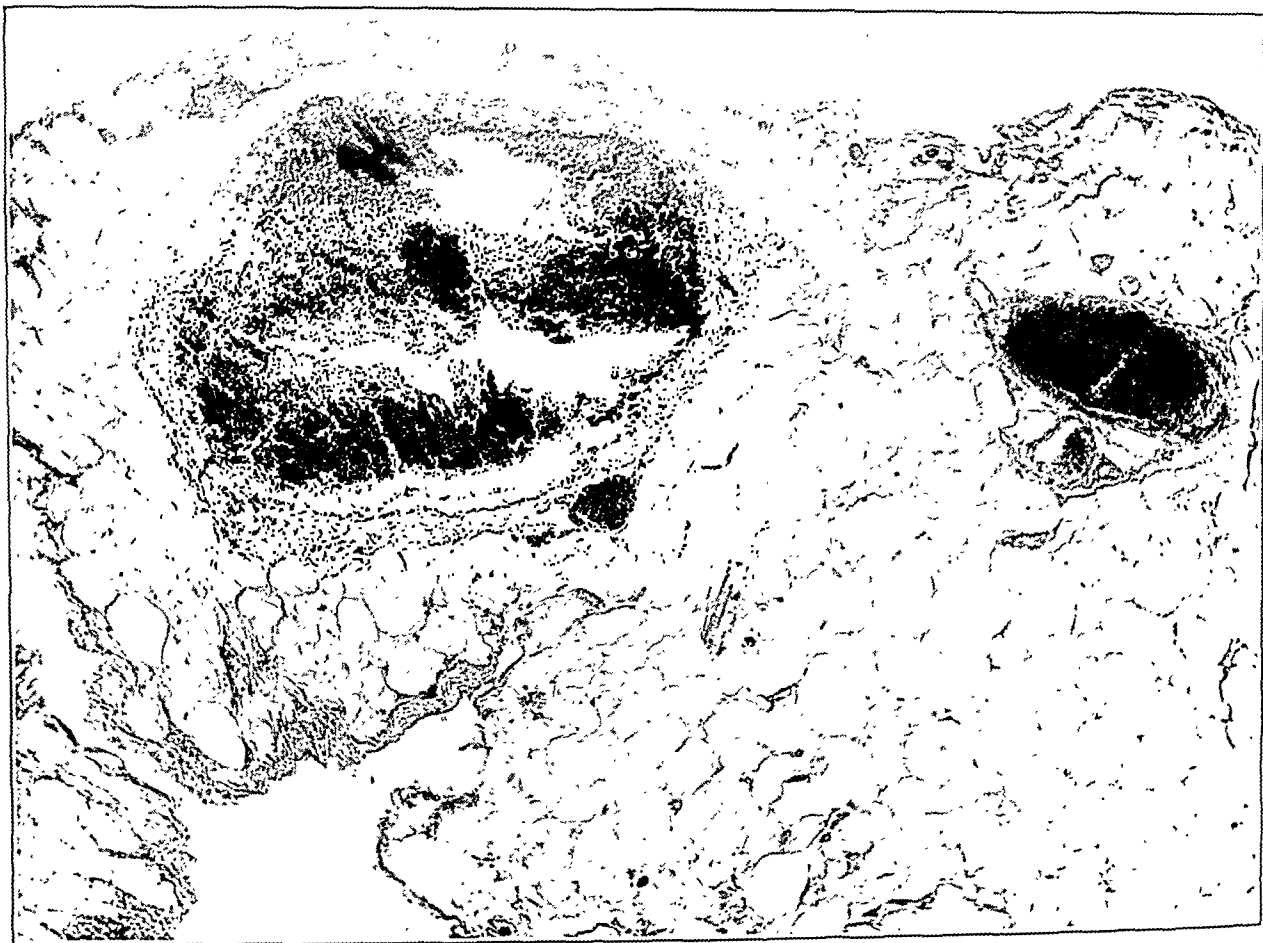


Fig. 6.—Section through omental ball from omentum in case 3 showing marginal endothelial hyperplasia with little hemorrhage or extravasation; reduced from $\times 60$.

changes comprised a circumscribed, knobby area of thickening at the dependent margin of the omentum (fig. 3). The red, congested edematous appearance so characteristic of complete torsion was not in evidence, the natural color of the omentum being preserved, and the sole departure from normal seemed to be one of consistency only. The microscopic section of this specimen also showed a distinctively different picture in that there was a striking absence of interstitial

extravasation and hemorrhage although there was some indication of vascular stasis and early thrombosis. There may be noted, however, in this section a characteristic thickening and endothelial hyperplasia along the margins of the mass (fig. 6). This is then a definite organic structural change which has not been observed in the acute complete types and which is no doubt to be interpreted as the result of repeated mild irritations to which the latter types are not exposed.

ETIOLOGY

In considering the etiology of omental torsion, it is of primary importance to determine whether or not the causative factors are intrinsic or extrinsic. Does the omentum itself possess the power, under certain conditions, to initiate the twisting process; is this process dependent on forces exerted by adjacent structures, or are both these influences concerned in producing the conditions observed?

It is interesting to note that although the available experimental evidence is conservative, tradition has been generous in attributing to the great omentum a great variety of qualities and functions. Tait called it "the arbiter of peritoneal tides," while Robinson is responsible for the appellation "policeman of the belly." Among the older writers all manner of bizarre virtues were given to it. Heusner⁵⁰ summarized the views held up to the present as follows:

- (1) An apron protecting the intestines from cold (Aristotle).
- (2) A fixation ligament for the transverse colon (Versalius).
- (3) Protects abdominal viscera from friction (Verboyen).
- (4) Draws filled stomach downward, facilitating respiration (Hansen).
- (5) An organ separating and moistening the viscera, as well as an organ of absorption.
- (6) An expanded lymph gland exercising the functions of the hemolymph tissues of the abdomen.
- (7) A protective and defensive agent in various pathologic conditions and accidents.

According to the most modern conceptions, based on extensive clinical observations, the omentum is endowed with a spontaneous ameba-like movement—an "intelligent chemotaxis"—through which it exercises the power to plug openings in a ruptured viscus, limit inflammatory processes and even act as an hemostatic agent in cases of intra-peritoneal hemorrhage.

The existence of an intrinsic "intelligent chemotaxis" in the great omentum was, however, called into question by the experimental studies of Rubin,⁵¹ who concluded that the sole functions of this structure

50. Heusner: *München. med. Wchnschr.* **52**:1130, 1924.

51. Rubin: *Surg., Gynec. & Obst.* **12**:117, 1911.

are: (1) to afford fixation for the intestine; (2) to provide freedom of intestinal movement, and (3) to serve as a vehicle for the arteries, veins and nerves. These studies suggest that the omentum does not invariably repair defects, that whatever protective power is displayed depends on its properties as peritoneum and that its usefulness in inflammatory lesions is due to its power (*a*) to form adhesions isolating and rendering innocuous the effects of inflammation and (*b*) to absorb and eliminate the toxic products. So far as "intelligent chemotaxis" is concerned, the displacements of the omentum are explained as due to (1) intestinal peristalsis, (2) intra-abdominal tensions, (3) the suction action of the diaphragm and (4) distention of the stomach and colon by gas or fluid. In the presence of free intraperitoneal fluid the omentum is invariably curled up on its surface and is usually found on the anterior face of the liver when there is a large amount of fluid. For the purposes of the present discussion, therefore, the net result of these experiments serves to discredit any intrinsic power of the great omentum to initiate the twisting movement through which the condition of torsion is brought about. Extraneous influences must be sought in explanation of the phenomenon of torsion, which is to say that this condition presupposes the presence of a concomitant intra-abdominal pathologic process.

In seeking to establish the nature of the extraneous factors leading to omental torsion, it is of importance to point out that the great omentum normally presents certain structural characteristics which have a contributory influence. This structure varies in length from a few inches to an enormous elongated mass reaching deep into the pelvis. Meckel is authority for the statement that it passes into the pelvis in 25 per cent of males and in 50 per cent of females. The right border is longer and much more mobile than the left, which is usually found tucked up in the left hypochondrium. In addition, the right side is frequently distinguished by the presence of two or more tongue-like processes; this fact, together with the greater length and mobility on the right side, is significant in view of the prevalence of torsion on this side. General body nutrition is accurately reflected by the omentum; in emaciated persons it is thin and shriveled, while in those who are well nourished or obese there is an early and rapid accumulation of fat in the organ which may attain tremendous weight, size and thickening. In this connection the discussion of a "torsion habitus" is to be recalled. Finally it was shown by Payr, who carried out experimental studies to determine the causes of torsion, that the disposal of the omental circulation was such as to favor the twisting process. According to this observer, the omental veins are unusually long and tortuous and when, for any reason, they become engorged there is a tendency toward their spiral rotation about the shorter rigid artery acting as a mesentery, so that the first step of torsion may thus be initiated.

Pathologic changes in the omentum and in its environment constitute the actual causative factors of torsion, but these factors are not necessarily identical for all the recognized varieties of torsion. For example, the mechanics of torsion when a weight is suspended free at the end of a string (unipolar torsion) are quite different from the conditions that obtain when a handkerchief is suspended by diagonally opposite corners with freedom of rotation between these fixed points (bipolar torsion).

In principle, conditions favorable for unipolar torsion are presented by any local increase in omental density capable of producing a narrowing and lengthening of the omentum until it is suspended by a true pedicle. There is then lacking only the proper stimulus to initiate the twisting process. The statement has been made by Baldwin⁵² that all that is necessary for this type of torsion is the existence of a pedunculated omental tumor with no mechanical obstacles to rotation.

Concerning this omental tumor mass, three distinct types and manners of origin may be distinguished: (1) It may be a true tumor of a neoplastic variety; (2) it may be due to an inflammatory fibrosis secondary to an acute process in an adjacent structure, e.g., the appendix, and (3) it may be produced by the mechanical forces of an omental hernia.

Of the true omental tumors, the embryonal lymphangioma, a cystic growth encountered in early life, appears to be most frequently associated with torsion. According to Fink,⁵³ thirty-eight of these tumors had been reported up to 1914, and in the present series there were three instances of torsion due to this type of tumor. Prutz⁵⁴ found that torsion occurred with sarcoma, secondary carcinoma and echinococcus cysts. In a case reported by Owen,⁵⁵ a hydatid cyst had produced a definite torsion of the omentum with multiple twists of the pedicle.

Inflammatory tumors of the omentum are produced by secondary extension from an adjacent focus, e.g., the appendix. These tumors persist in the omentum as localized areas of fibrosis long after the original focus has subsided or has been removed and may thus become the starting point for a torsion of the omentum. My case 3 was an instance of this sequence of events.

Four years previous to the onset of the symptoms of torsion, this patient, a large obese man, was operated on for acute appendicitis requiring drainage. At the second operation for torsion a characteristic localized area of fibrosis was identified as responsible for the twisting pro-

52. Baldwin: *Prag. med. Wchnschr.* **35**:559, 1910.

53. Fink: *Surg., Gynec. & Obst.* **15**:70, 1914.

54. Prutz: *Deutsche Ztschr. f. Chir.* **46**:280, 1913.

55. Owen: *Intercolon. M. J. Australasia* **2**:459, 1921.

cess. It appears logical to regard this omental tumor as a secondary manifestation of the antecedent appendical inflammation. In my case 1, acute complete omental torsion was found to be associated with definite evidence of subsiding acute inflammation of the appendix. Analysis of the cases in this series discloses thirteen other instances in which some form of acute or subacute lesion of the appendix either preceded or was coexistent with the torsion. These cases were all classified as torsion secondary to inflammatory tumors of the omentum on the assumption that an infective process adjacent to the omentum had induced a localized reactive fibrosis which, in turn, accounted for the progressive steps leading to torsion. It seems probable that this sequence of events obtains more frequently than the foregoing figures indicate and that other organs, such as the gallbladder, stomach or pelvic structures, may, in a similar manner, set up localized reactive omental tumors which persist, to cause trouble, long after the original causative focus has ceased to exist.

The third, and undoubtedly the most common, source of localized omental fibrosis and pedicle formation is the long-standing inguinal hernia. It is a well recognized clinical fact that these herniae bring about an actual lengthening of the omentum, a portion of which eventually comes to lie in the scrotum. According to Prutz, the portion of the omentum in the scrotum is exposed to comparatively little pressure while that in the inguinal canal is compressed into a roll or cord which gradually becomes thinner as the scrotal portion becomes edematous and thickened in consequence of the compression above. The resulting tumor mass suspended by its long thin pedicle now presents conditions ideal for unipolar torsion if the proper initial twisting impulse is added. Repeated attempts at reduction of this mass frequently supply this necessary impulse. The movement of the omental mass back and forth through the unequally calibrated inguinal canal has been compared by Hadda to the rotation of the fetal head passing through the parturient canal or to a bullet forced through the bore of a pistol barrel. Attempts of the rigid, fibrosed tumor to adjust itself to the varying diameters of the inguinal canal impart a rotatory motion to the advancing tumor, and this turning movement is accentuated by the fibers of the transversalis and oblique muscles. These twisting movements, however mild, lead progressively to further edema and fibrosis of the tumor, the increasing size and weight of which accentuate the degree of twist; a vicious circle is thus produced, which determines the final stages of complete torsion.

In the pure abdominal, unipolar types of torsion, Hadda's theory of the initial twisting impulse is obviously not applicable. It has been said of this type that, given a pedicled tumor, all that is necessary for

torsion is the absence of mechanical obstacles to rotation. Nevertheless it is evident from a study of certain histories that definite factors play a part in initiating this rotation when the proper relation of pedicle and tumor exists. For instance, there were thirty-one cases of abdominal torsion in the series in which the onset of acute manifestations coincided strikingly with such occurrences as blows on the abdomen, violent coughing spells, horseback riding, dancing, being violently whirled about while wrestling, stooping over a tub and various other sudden physical efforts. In these cases a preexisting pedicled tumor of the omentum is assumed, "with no mechanical obstacles to rotation"; under these conditions it is entirely conceivable that such a combination of events is competent to precipitate the rotation necessary to determine a complete torsion. Prutz thought that a change in the position of the entire body was sufficient, under the influence of gravity, to supply the necessary impulse. In the cases reported by Morestin and Taddei, torsion was attributed to violent peristalsis induced by drastic catharsis. Kraske,⁵⁶ observed a case in which omental torsion was said to be due to the failure to rearrange the omentum after a protracted operation in the Trendelenburg position. While the relationship of some of these factors to torsion many well be questioned, it is nevertheless fairly definitely established that, given a free, pedicled omental tumor, a number and variety of forces enter into the production of the initial rotatory movement.

As has been noted, bipolar torsion presents mechanical conditions quite different from those of unipolar torsion, and those conditions favorable for the former type are established when a tongue of the free margin of the omentum becomes fixed or adherent to some adjacent intra-abdominal structure. This abdominal point of fixation is, in the majority of instances, the result of a localized inflammation in the structure to which the omental tip becomes attached. The appendix, gallbladder, ovaries and tubes play the largest part in this process, but infrequently fixation is noted at the uterus, right kidney, ascending colon and stomach. Formation of the second fixed point by purely mechanical means is suggested by the experience of Lockett who encountered a bipolar torsion in a patient operated on ten years before for right inguinal hernia. The twisted tongue of omentum in this case was adherent to the old hernial cicatrix, and the author concluded that the original operator had included a tongue of omentum within the ligature used to tie off the hernial sac. This experience in particular and the principle of bipolar torsion in general suggest that the deliberate fixation of a portion of the omentum by suture to an adjacent organ is not without danger, and that the accidental fixation which may occur during closure of laparotomy wounds is to be avoided carefully.

56. Kraske, quoted by Aimes (footnote 5).

Given the two fixed points of bipolar torsion, there is still to be determined the character of the impulse which initiates rotation about the axis thus formed. Payr and Frederick observed cases of bipolar torsion in which the omental tip was adherent to an ovarian cyst. Primary torsion developing in the latter was thus transmitted to the omentum causing a secondary bipolar torsion therein. This type of causation is, however, obviously infrequent, and it is entirely probable that the exciting factors of rotation in bipolar torsion are not unlike those described for unipolar torsion, viz., changes in the position of the body, blows on the abdomen, sudden severe physical strains, hyperperistalsis of the intestine, etc.

CONCLUSIONS

Marchette reported the first case of torsion of the omentum in 1851. Corner and Pinches, in 1905, collected 54 cases, which included 3 of their own. A careful search of the literature from that date to 1929 yielded 164 additional cases, to which I add 3 personally observed cases for a total of 217. It has been my purpose in this report to assemble the clinical and pathologic data presented by this group and on that basis to evaluate the clinical importance of torsion of the omentum. As a result of this study, it is possible to summarize briefly the salient features of this condition in the following conclusions:

1. The normal environment and anatomic arrangement of the great omentum are such as to favor rotation of this structure about its long axis, while the introduction of certain mechanical conditions and pathologic changes within and adjacent to it supply the immediate exciting causes of such rotation.

2. It is clearly established that omental twists are capable of producing clinical symptoms of an acute and chronic character, and that this condition therefore merits some consideration in the diagnosis of abdominal conditions.

3. Variation in the intensity of degree of rotation determines two basic clinical and anatomic types of torsion: (1) the complete, in which acute, progressive symptoms and marked pathologic changes are dependent on complete permanent circulatory obstruction at the site of twist, and (2) the incomplete, which is characterized by vague, chronic recurring symptoms and mild pathologic changes in consequence of incomplete, partial or temporary obstruction which permits repeated spontaneous restitution before pronounced organic changes develop.

4. Diagnosis presents obvious difficulties as indicated by the fact that a correct preoperative diagnosis was recorded in only 7.9 per cent of 217 cases. A statistical study of the series, however, emphasizes

certain essential clinical manifestations and points of history, the recognition of which should enhance the precision of a preoperative diagnosis.

5. The deliberate fixation of the free margin of the omentum by suture to an adjacent structure may be the source of future complications, and its accidental inclusion during abdominal closure is to be avoided carefully.



Fig. 7 (case 4).—Photograph showing the narrow tight pedicle and the distal gangrenous mass of the omentum.

NOTE.—The following case of omental torsion was encountered shortly after the submission of this article for publication.

CASE 4.—G. W., aged 47, a barber, was admitted to the fourth surgical division, Bellevue Hospital, on April 1, 1931, with a condition diagnosed as acute appendicitis. Three days before admission he had noted a dull pain in the right lower quadrant of the abdomen. The pain was constant, did not radiate and was not accompanied by nausea, vomiting, diarrhea or urinary disturbances. The appetite had remained good, although the patient had been markedly constipated during the week preceding the attack. He had never experienced similar attacks, and the previous history was unimportant.

Examination disclosed a robust, obese man who weighed 190 pounds (86.2 Kg.). General physical examination gave negative results. The abdomen was protuberant and lax. There was marked, acute, localized tenderness over McBurney's point, but no muscular spasm could be detected. In this same region a small, hard, painless and freely movable mass was palpable. There was no gross evidence of free fluid. The temperature was 100.6 F.; the pulse rate, 100. There were 9,550 white blood cells, with 72 per cent polymorphonuclears. Urinalysis gave negative results. A diagnosis of acute appendicitis was made, and immediate operation was advised.

Operation.—When the peritoneum was opened, a small amount of free sero-sanguineous fluid was found. The appendix was decidedly injected, and the gross appearance justified a diagnosis of subacute appendicitis. Exploration was extended, however, and resulted in the finding of a hard mass above and to the right of the incision. On delivery, this proved to be a bluish triangular mass of omentum about the size of a human hand. Its pedicle was thin and tightly constricted and could not be untwisted. The mass swung free in the peritoneal cavity; it was not attached to any other structure, and it was apparently not associated with the appendix. There was no inguinal hernia.

This case evidently represents a good example of pure abdominal torsion of the primary type.

CONGENITAL CYSTIC DILATATION OF THE COMMON BILE DUCT

REPORT OF A CASE AND REVIEW OF THE LITERATURE *

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Cystic enlargements of the common bile duct have been variously described as congenital, idiopathic and acquired. They have been called cysts, cystic dilatations and diverticulae of the duct. The etiology of the condition is obscure, and although many explanations have been offered, none of them seems to be completely satisfactory. Correct diagnosis before operation was apparently made only three times in the eighty-three cases recorded, and in many instances, the true condition was not recognized even at operation. Such errors will doubtless be repeated in the future, for few surgeons actually see a patient with this lesion. Therefore, unless the clinical picture is clear in the mind of the observer, it is unlikely that a correct preoperative diagnosis will be made. In contrast with this frequent failure in diagnosis, the methods of treatment have steadily improved, so that in the more recent cases, even when surgeons were not familiar with the results obtained in the past by different methods, successful procedures have been carried out with increasing frequency.

In the case to be described, certain features were found which indicated that the condition was of congenital origin. This report, therefore, may be of value in helping to determine the etiology.

REPORT OF CASE

History.—F. L. C., a Chinese woman, aged 40, was admitted to the medical service of the Peiping Union Medical College Hospital on Sept. 25, 1929. The principal complaints were pain in the epigastric region and vomiting. According to the history, she had been entirely well until four or five years previously, when she first started to have pain in the epigastrium. This, she said, was intermittent, dull and aching, and did not radiate. It usually came on from thirty minutes to an hour after eating, and was often relieved by vomiting. So far as she knew, there had never been fever or jaundice. She had found that pressure on the epigastrium, bending the body and needling the abdomen (a common practice in China) tended to reduce the severity of the pain.

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About six weeks before admission, the symptoms became greatly exaggerated. The pain was almost continuous, and at times it was so severe that the patient was said to have lost consciousness on several occasions. The vomiting also became almost continuous. Fever and chills were frequent. There was no jaundice. The stools were of normal color and consistency.

Examination.—On examination, it was noted that the patient was somewhat emaciated and looked quite sick. She was apparently having considerable pain in the abdomen. Her lips were pale and dry, and the tongue was coated. The heart and lungs were essentially normal; the blood pressure was 92 systolic and 44 diastolic. The temperature was 38 C. (100.4 F.); the pulse rate, 120, and the respiratory rate, 24. The lower half and the right upper quadrant of the abdomen showed fulness. The swelling in the lower portion of the abdomen was due to an enlarged uterus, the patient being in the fourth month of pregnancy. The abdominal wall moved normally during respiration. In the right upper portion of the abdomen, there were muscle spasm and tenderness on palpation, but a definite mass could not be felt or outlined by percussion. The liver and spleen were not felt. The upper margin of the uterus could be palpated midway between the symphysis and the umbilicus.

Laboratory examinations showed the urine and stools to be normal. Examination of the blood showed: red cells, 4,100,000; hemoglobin, 93 per cent, and white cells, 5,250, with polymorphonuclear cells, 60 per cent; lymphocytes, 36 per cent, and large mononuclear cells, 4 per cent. The icteric index was 5 units, and the van den Bergh test showed only a trace of bilirubin.

The tentative diagnosis was subacute perforation of a gastric or duodenal ulcer or disease of the gallbladder. A roentgenologic examination of the stomach was requested. This examination showed that the pyloric end of the stomach was irregular; the duodenal bulb was small, contracted and not well filled. The first portion of the duodenum was narrowed; the second portion was dilated, and there was marked duodenal stasis. There were hypotonicity and decreased motility of the stomach. Sodium tetra-iodo-phenolphthalein was given by mouth, but a shadow was not seen in the region of the gallbladder either thirteen or eighteen hours after ingestion. The roentgenologic observations were suggestive of extensive adhesions in the region of the pylorus and duodenum, probably due to an inflammatory lesion of the gallbladder.

The patient was transferred to the surgical service on September 27. On the previous night she had had a chill, after which the temperature was 40 C. (104 F.). The white blood cell count made at that time showed only 2,800 cells. On September 27, there was marked tenderness with muscle spasm in the right hypochondrium, and an indefinite, tender mass was felt about 3 cm. below the costal margin. This was thought to be either a tender, enlarged liver or a distended gallbladder. There was no jaundice. A diagnosis of acute cholecystitis with hydrops of the gallbladder was made. The patient was operated on on the following morning.

Operation.—A right rectus incision was made, and the peritoneal cavity was found free from fluid. The stomach was displaced downward and to the left by a large reddened mass which lay between the lower margin of the liver and the stomach. Exploration of the pelvis showed the uterus to be enlarged and soft (the patient was four months pregnant). No abnormalities were felt. The liver was practically normal in size, and was essentially normal in appearance and consistency except for a few whitish scars on its surface. Of great interest was a large, reddened, more or less spherical mass which lay between the liver and the stomach and duodenum. There were no adhesions surrounding it, but it was

quite red, and there was edema of its walls. The duodenum curved downward somewhat anterior to the mass; exploration showed that it lay anterior to a patent foramen of Winslow. The mass was evidently cystic. The gallbladder was slightly enlarged. Its wall was thickened and somewhat edematous, and it soon became apparent that the bladder communicated directly with the cystic mass through a large cystic duct. Palpation indicated, however, that although the outside diameter of the cystic duct was large its lumen was probably rather narrow. It seemed fairly obvious that we were dealing with an infected cyst of the common bile duct. The hepatic ducts could not be made out, the rounded mass coming off almost directly from the under surface of the liver. The head of the pancreas could be felt below the cyst and was apparently of normal consistency. Stones could not be felt within the gallbladder or within the cyst. Pads were placed to wall off the abdominal cavity, and a purse string suture was laid in the anterior wall of the cyst. A needle was inserted, and 450 cc. of slightly turbid bile was aspirated. As this was done, the cyst and the gallbladder collapsed. The cyst was then incised. The wall was about 7 mm. thick and was very vascular. It seemed to consist of two layers, an outer layer of loose areolar connective tissue richly supplied with blood vessels and a more dense inner layer. The interior of the cyst showed a few superficial ulcerations. It could not be determined grossly whether or not it was lined with mucosa. An effort was made to find the opening from the cyst into the duodenum, but this could not be discovered.

Digital exploration within the cyst failed to reveal the presence of stones. Although the patient had not had jaundice and the cyst was presumably draining into the duodenum, in the presence of the infection, it was thought advisable to secure more adequate drainage, but not to drain the bile to the exterior. The lower margin of the cyst was then dissected from the duodenum over a small area, and a lateral anastomosis was made between it and the duodenum, the stroma being about 1 cm. long. The suturing was done with a continuous lock stitch of no. 1 chromic catgut, reinforced anteriorly by mattress sutures of silk. When the duodenum was opened, there was bile-tinged fluid within its lumen. A finger was inserted through the opening in the duodenum, but even on bimanual palpation from the inside of the duodenum and the inside of the cyst, the papilla of Vater could not be located. Stones were not felt. An effort was then made to find the hepatic ducts. Viewed from the inside of the cyst, two ducts from the liver could be seen opening directly into it. These ducts were not dilated. In order to reduce the size of the cyst and also to secure tissue for microscopic examination, an elliptical area was excised from the anterior wall of the cyst. This opening was closed with a continuous lock stitch of no. 1 chromic catgut reinforced with a continuous right-angled suture of medium silk. One cigaret drain was placed down to the vicinity of the suture line, and the abdomen was closed tightly with interrupted silver wire sutures.

Course.—The patient stood the operation well. Her pain was almost entirely relieved, although she complained of discomfort at the site of the incision. She presented evidence of acidosis. There was an odor of acetone to the breath, and the urine contained acetone and diacetic acid. Blood taken at this time showed a carbon dioxide-combining power of 41.2 per cent by volume. She was given a solution of dextrose intravenously, subcutaneously, by mouth and by rectum, and her condition improved greatly.

From the bile obtained at operation, a pure culture of *Bacillus paratyphosus* A was grown. A Widal test made on September 30 showed agglutination to a dilution of 1:160 with this organism. Repeated blood cultures produced no organisms.

The abdomen remained soft; the drain was removed in forty-eight hours, and the wound healed per primam intentionem. The temperature fluctuated considerably, but showed a tendency to return to normal. The white blood cell count remained low. The spleen could not be palpated. The patient continued to look very sick, although she said that she felt well.

On October 5, vomiting began and persisted in spite of all attempts at control. Acidosis again developed and could not be controlled. The patient went into a state of collapse; she died on October 9, eleven days after operation. On October 8, a positive culture of *B. paratyphosus* A was obtained from the stools. On the same day, the Widal test showed agglutination with this organism to a dilution of 1:1,280.

Autopsy.—The outstanding observations at autopsy, which was performed fourteen hours after death, were as follows:

Gross Description: The body was that of a greatly emaciated Chinese woman of middle age. In the right rectus region was a long, recently made surgical incision tightly closed by wire sutures. When this incision, through which it was necessary to perform the autopsy, was opened, the underlying abdominal viscera were found to be bound to the anterior abdominal wall by a layer of fibrin within the meshes of which was considerable purulent exudate. There was a large cystic mass about 10 cm. in diameter lying in apposition to the right inferior surface of the liver, to which the pyloric end of the stomach, the duodenum, pancreas, transverse colon and omentum and several loops of ileum were closely bound by a massive amount of fibrinopurulent exudate. The gallbladder was not seen. In the dome of the cystic mass, which was adherent to the abdominal wall, was a slightly elliptical opening, 4 cm. in diameter with slightly everted edges, from which hung a number of black silk sutures. The omentum was closely plastered about the edges of this mass of adherent structures. The remaining peritoneal surfaces were smooth and glistening. The abdominal cavity contained no free fluid. Within the uterus, which extended to the umbilicus, a fetus was easily palpated. The spleen was small and firm.

The liver was of about normal size, rather soft and a mottled, grayish brown. The capsule of the left lobe and the anterior surface of the right lobe were smooth and glistening, but the inferior surface of the right lobe, which was densely adherent to the large cystic mass already mentioned, was covered by a thick layer of fibrinopurulent exudate. On the superior surface of the liver, a number of dark red, sharply outlined zones, each about 1 cm. in diameter, which appeared to be hemorrhages, were seen within the underlying tissue. On section, the cut surface was seen to be a mottled, grayish brown; the lobules were swollen and rather indistinct in outline. Throughout the liver were a number of small, dark red, hemorrhagic zones, each embracing several lobules. In addition, countless opaque, yellowish-gray points, each less than 1 mm. in diameter, were seen, all of which seemed to lie in portal areas. Occasionally such a structure somewhat larger than the rest was seen which had a soft, purulent, bile-stained center.

In studying the mass of structures matted together with fibrin at the hilus of the liver, the duodenum was first opened. Its mucosa was deeply stained with bile and was intact except for a small opening in its posterior wall 1 cm. in diameter by which it communicated freely with the adjacent cyst. The margins of this opening were apparently completely covered by mucosa, and a number of black silk sutures were found binding the duodenum to the wall of the cyst in this region. The stomach and transverse colon were next opened and were found to be of normal appearance. The neck and proximal segment of the gallbladder, measuring 2.5 cm. in length and 8 mm. in diameter, were found to lie embedded in fibrin

closely adherent to the superior and anterior surface of the cyst. The fundus and distal segment, measuring 4 cm. in length and 1.5 cm. in diameter, after making a sharp bend posteriorly, lay collapsed between the wall of the cyst and the liver. When the gallbladder was opened, the proximal segment was found to contain about 1 cc. of thin green bile. The wall was moderately thickened, but the mucosa of the entire structure was intact and of normal appearance. By an opening 5 mm. in diameter, the gallbladder passed directly into a somewhat tortuous, tubular structure 1.5 cm. in length and from 3 to 4 mm. in diameter. This structure seemed to correspond to the cystic duct, but had an unusually thick wall (from 1 to 2 mm.) and was lined by mucosa similar to that seen in the gallbladder. No valvelike folds were present in its mucosa. This unusual cystic duct led directly, by an opening 1 cm. in diameter, into a large cystic cavity averaging about 8 cm. in diameter, the tough, stiff wall of which varied from 1 to 5 mm. in thickness. The cyst was partially divided from above and posteriorly by a low septum, 2.5 cm. in length and 2 cm. in height, into two compartments. The cystic duct opened into the right compartment, and in the posterior wall of the left compartment, separated by a distance of only a few millimeters, were found the elliptical openings of two large hepatic bile ducts. The interior aspect of the inferior portion of the cyst presented a communication, 1 cm. in diameter, with the duodenum, the result of surgical intervention. To the right of this opening was a conical pouch leading in the direction of the head of the pancreas. When this pouch was explored, a small opening about 1 mm. in diameter, partially guarded by a small, thin fold of soft tissue projecting from the wall of the cyst, was seen. A probe could not be passed into this orifice, but when it was opened carefully with scissors, a duct 3.5 cm. in length, with a thin wall and a lumen 1.3 mm. in diameter, was found passing slightly diagonally to the left through the pancreas, and opening into the duodenum by an elliptical orifice 2 mm. in length. At a point 7 mm. distant from the wall of the cyst, this duct was joined by the pancreatic duct. There seemed to be no doubt that the small structure connecting the cyst with the duodenum was at least a portion of an anomalous common bile duct. It was of approximately the same diameter throughout its course and appeared to be covered by mucosa. Its wall was very thin and delicate (fig. 1).

The cyst contained only about 3 cc. of thin, slightly turbid bile. Its lining was smooth and bile-stained throughout, having a rather velvety appearance, as if it were covered by mucosa, but showing a number of irregular shallow ulcers.

The inferior surface of the right lobe of the liver showed a marked degree of atrophy as the result of pressure by the cyst. When the larger branches of the hepatic bile ducts were dissected from their two openings into the cyst far back into the liver substance, they were found to be unaltered. No macroscopic changes were noted in the smaller bile ducts. Although the portal vein appeared to have been somewhat compressed by the posterior aspect of the cyst, no further changes were noted in it, nor was there appreciable dilatation of the splenic and mesenteric veins.

Aside from a few loops of ileum and a portion of colon adherent to the cyst at the hilus of the liver, the peritoneal surface of the intestine was smooth and glistening. A few of Peyer's patches in the lowermost portion of the ileum were slightly swollen and showed occasional shallow ulcerations. Otherwise, the mucosa was not remarkable. No parasites were present. The mesenteric lymph glands were unaltered.

The spleen weighed 80 Gm. It was quite small, dark red and rather firm. On section, the malpighian bodies were inconspicuous, the connective tissue was somewhat increased, and the rather dry pulp was scraped away with difficulty.

There was a moderate degree of brown atrophy of the heart. The aorta showed early arteriosclerosis.

The lungs were voluminous and dark red. On section, they were moist and engorged with blood.

The pancreas and suprarenal glands were not remarkable.

The kidneys were of normal size and consistency. There were a few small scars on the surface; otherwise, they were not altered.

At the request of the patient's family, the uterus, ovaries, fallopian tubes and brain were not removed. The uterus extended to the level of the umbilicus, and a fetus within it was readily palpated. The ovaries and fallopian tubes were of normal appearance. The corpus luteum of pregnancy was found in the right ovary.

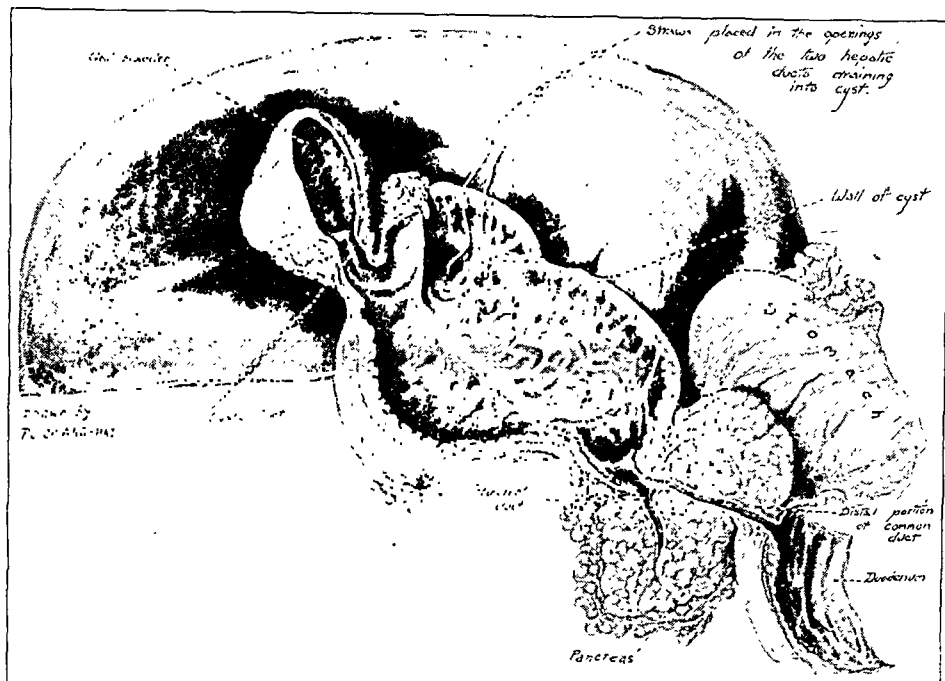


Fig. 1.—Sketch of specimen taken at necropsy, showing the relation of the cyst to the gallbladder, the hepatic ducts and the terminal portion of the common bile duct.

Microscopic Examination: The gallbladder was lined by mucosa composed of long, irregularly shaped, characteristic villi covered by a single layer of columnar epithelium. The mucosa was infiltrated with a few polymorphonuclear leukocytes and a moderate number of small mononuclear cells. The mucosa lay on a thick, loose, musculo-elastic layer which was in turn covered by a thin adventitia of connective tissue. Both the musculo-elastic layer and the adventitia contained many arteries, veins and nerves and were infiltrated slightly by lymphocytes and other small mononuclear cells. Glands were not seen in the wall of the gallbladder.

Sections of the cystic duct showed the same general characteristics as those of the gallbladder. It was found to be lined completely with mucosa, the villi of which were somewhat more slender and less irregular than those of the gallbladder, but were also covered with low cylindric epithelium. Infiltration by polymorphonuclear leukocytes and mononuclear cells was somewhat greater than

in the gallbladder. The musculo-elastic and adventitial layers were directly continuous with those of the gallbladder and were of the same character, but both layers showed considerable increase in thickness due to diffuse growth of connective tissue, and the cellular infiltration was somewhat more intense. The bundles of smooth muscle were just as large and as numerous as in the wall of the gallbladder, but were somewhat more widely separated by connective tissue and infiltrating cells.

The best sections of the wall of the cyst were made from a large, freshly fixed portion removed for study at the operation. The piece of tissue measured 8 by 5 by 0.8 cm. and was removed from the site of the opening in the dome of the cyst already described. Although it could not be stated exactly which part

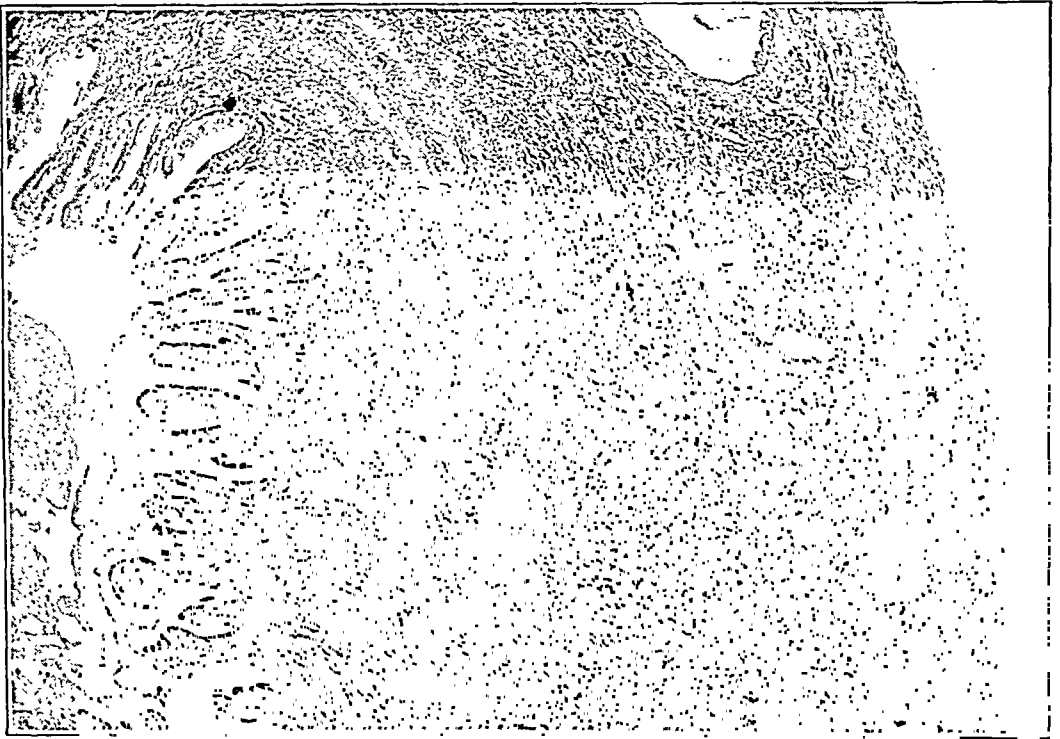


Fig. 2.—Section of a portion of the anterior wall of the cyst removed at operation, showing a well preserved mucosa and a great thickening of the wall. The concentric homogeneous layers of tissue consist of smooth muscle fibers. The remainder of the wall is composed of connective tissue and infiltrating cells; $\times 30$.

of the wall of the distended cyst this tissue represented, it was clear from the contracted specimen that it was at least 3 cm. distant from the opening of the cystic duct.

One of the sections from this piece of tissue showed the cyst in this area to be completely lined with mucosa in all respects similar to that of the gallbladder and the cystic duct (fig. 2). The tips of many of the villi were necrotic and infiltrated with leukocytes, and overlying large areas of the mucosa was a thick layer of fibrin, leukocytes and debris. A few short, gram-negative bacilli in small clumps and also occasional gram-positive, slightly oval bacteria occurring mainly in pairs and short chains were seen within this exudate. Bacteria were not seen

within the underlying tissues, though the mucosa was densely infiltrated with leukocytes and wandering cells. Beneath the mucosa was a thick layer composed of large bundles of smooth muscle interlacing with elastic fibers and rather widely separated by a loose meshwork of fibrous tissue. Infiltration by lymphocytes and larger mononuclear cells was intense. Beyond the musculo-elastic layer was a very thick layer of dense fibrous tissue composing more than half the total thickness of the wall of the cyst. This layer contained many greatly dilated blood vessels and was also heavily infiltrated with mononuclear cells. A number of large phagocytes filled with granules of hemosiderin were also present. On the surface of the adventitia were a few strands of freshly formed fibrin.



Fig. 3.—Inner layer of the wall of the cyst from an area not showing mucosa. Marked chronic and acute inflammatory changes are present. Many large bundles of smooth muscle fibers embedded in dense fibrous tissue compose the greater part of the wall of the cyst; $\times 100$.

Eight other sections taken from all portions of the wall of the cyst showed essentially the same structure as that just described for the specimen removed at operation, the only differences being in the condition of the mucosa. Small villi somewhat less numerous than in the gallbladder and the cystic duct were found in all of the sections. Many of these were still covered with epithelium, which was generally of the low cuboidal variety. In many of the sections most of the epithelium was missing, but in all of them except one villi at least partially covered with epithelium were present. In this one section, taken from the inferior portion of the cyst, the lining consisted of a thick layer of granulation tissue showing

marked chronic inflammatory changes and covered by fibrinopurulent exudate (fig. 3). The structure of the musculo-elastic layer was retained in all of the sections. Through one long interval, including the entire gallbladder, cystic duct and entire anterior aspect of the cyst, the musculo-elastic layer was found to be in continuity. The varying thickness of the wall of the cyst was caused mainly by variations in thickness of the outer layer of connective tissue and the degree of cellular infiltration.

Throughout the sections of liver were striking small focal necroses situated in the portal areas and frequently adjacent to the smaller bile ducts. These lesions consisted of densely coagulated central areas composed of necrotic liver cells,

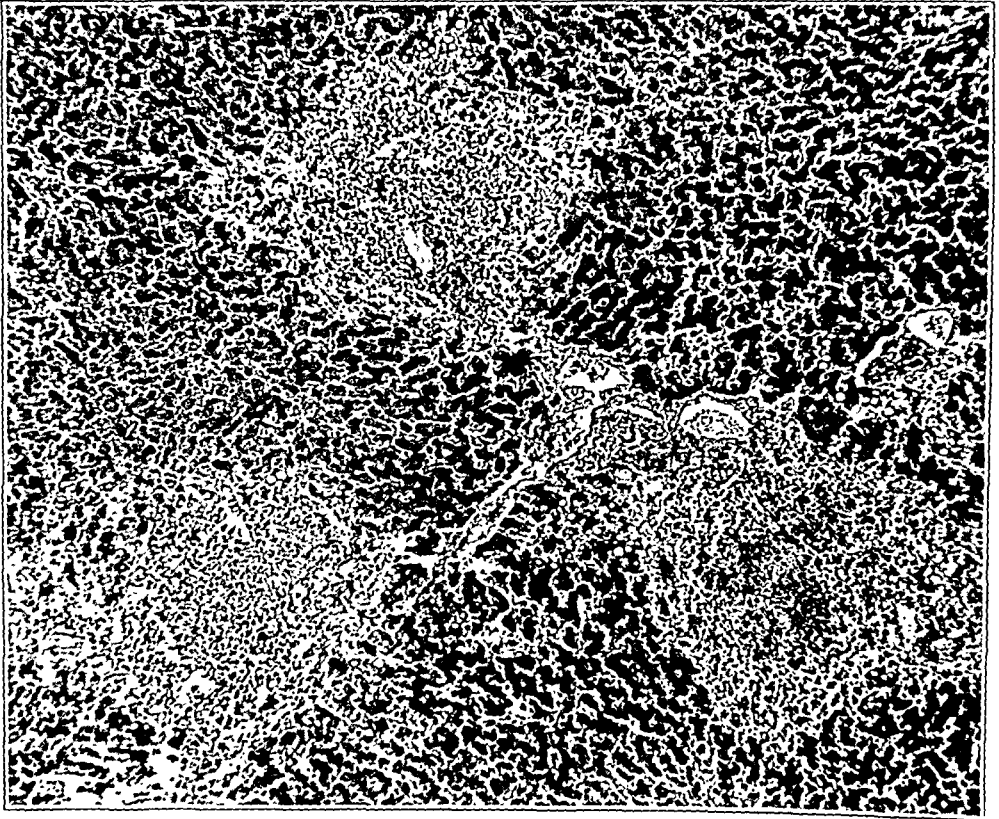


Fig. 4.—Focal necroses in the liver. Such lesions were found in each portal area; $\times 70$.

infiltrating leukocytes and mononuclear cells surrounded by a less dense zone containing partly necrotic, shrunken and fat-laden liver cells and a few leukocytes and wandering cells. Within this loose tissue were frequent hemorrhages. Several small abscesses within which were seen bile ducts and free bile pigment were also present. A few gram-negative bacilli were found in these abscesses. There were also a few small, fresh hemorrhages which appeared to arise in the portal areas. There was moderate diffuse infiltration with mononuclear cells and a few polymorphonuclear leukocytes about all of the smaller bile ducts, but none of them showed evidence of obstruction to the flow of bile. Many of the ducts, however, contained large clumps of small gram-negative bacilli.

There was slight hyperplasia of Peyer's patches, which showed superficial ulceration of the surfaces.

The mesenteric lymph nodes were unaltered.

The colon was normal.

The lungs showed a few patches of early pneumonia.

The stroma of the spleen was moderately increased. The venules were distended with blood.

The kidneys, heart, pancreas and suprarenal glands did not show changes of importance.

Comment.—The principal question of interest in this case is the nature of the cyst that comprised such a large portion of the extrahepatic biliary tract. It is clear that this structure replaced the greater part of the common bile duct, the entire hepatic duct and perhaps a portion of the cystic duct. There were no alterations in the intrahepatic ducts, which formed two main branches at the hilus of the liver and opened by separate orifices, without obstruction, into the cyst. From the inferior portion of the cyst a very narrow duct, the wall of which consisted only of a thin layer of mucosa and a few strands of connective tissue, led directly through the head of the pancreas into the duodenum. This narrow channel, evidently representing an anomalous common bile duct, was the only exit leading from the cavity of the cyst. An elongated structure representing the gallbladder and cystic duct was found with its fundus and the distal half of its body lying firmly compressed between the wall of the cyst and the under surface of the liver. The proximal portion of the gallbladder, evidently having been pulled forward and upward by the enlarging cyst, lay on the superior aspect of this structure, with which it connected by a wide opening.

It is impossible to say just how closely any of these structures correspond to the normal structures that they appear to represent, but it at any rate seems clear that the changes described were brought about by the operation of two factors, namely, congenital malformation and subsequent infection with bacteria.

The short, narrow common bile duct, which seemed to retain its original structure, was the only portion of the primary malformation that remained unaltered. While it seems a certainty that additional anomalies must have occurred in the development of the other portions of the extrahepatic biliary tract, the subsequent changes in these structures have been so great that an opinion as to the extent and exact nature of the original malformation does not seem justified. One feels safe in assuming, however, that the congenital stenosis of the intra-pancreatic portion of the common bile duct offered a constant obstruction to the flow of bile and thereby played at least a part in causing the distention of the proximal portions of the biliary tract, regardless of any congenital malformation that these structures may have suffered.

In view of the absence of jaundice in this case, one at first hesitates to consider the obstruction offered by the narrow common bile duct an

important factor in the production of the cyst. On the other hand, the lumen of the duct was so exceedingly narrow that an explanation of the failure of jaundice to appear is demanded before one can speculate further on the principles involved in the formation of the other changes. This explanation is apparently afforded by the large bands of smooth muscle found in all parts of the wall of the cyst, the contractions of which, it would seem, were adequate to force bile through the narrow common duct into the duodenum, thereby preventing the development of jaundice and at the same time temporarily relieving the pressure within the cyst. Thus it appears that obstruction to the flow of bile from the liver was prevented, though the constantly recurring distention of the extrahepatic biliary tract was followed by cystic dilatation of these structures. As suggested by the position of the gallbladder, a large portion of which was found to lie in approximately the normal position of this structure but compressed between the cyst and the liver, the size of the cyst must have increased greatly since the occurrence of the original malformation. It is hardly possible to account for any appreciable enlargement of the cyst on grounds other than obstruction to the flow of bile.

The other alterations shown by the cyst are clearly the result of long-standing bacterial infection of its contents. Proof of this is afforded by the enormous thickening of the wall of the cyst and by the growth of large amounts of connective tissue and heavy infiltration with mononuclear cells throughout all of its layers. Such an imperfect mechanism for discharging the bile as that which existed in this case was doubtless rendered still more inefficient by the added obstruction to the outflow from the cyst caused by inflammatory changes in the congenitally altered common bile duct, as well as by the increased viscosity of the infected, stagnant bile. Furthermore, it would seem that the subsequent gradual stiffening of the wall of the cyst by ever increasing connective tissue had rendered the discharge of its contents more and more difficult. An apparent desperate attempt on the part of the body to meet these difficulties is shown by the enormous hypertrophy of smooth muscle seen in sections taken from all portions of the wall of the cyst.

An added point of interest is the infection of the contents of the cyst with *B. paratyphosus* A, which seems to have been responsible for the illness of the patient. Though the widely spread ulceration of the mucosal lining of the cyst and other acute inflammatory changes seem clearly to have been caused by this organism, it is not unlikely that other organisms in the past played a part in the production of the more chronic changes. Whether the acute paratyphoid infection was only recently acquired or was an exacerbation of chronic infection of the cyst with this organism cannot be stated with certainty. The failure to recover

paratyphoid bacilli from the blood during the patient's entire stay in the hospital and the absence of any changes in the spleen are points that speak against a general paratyphoid infection. It seems more likely that a chronic infection of the cyst, favored by the ever increasing stagnation of bile, became active and spread widely through the liver by way of the bile passages. The low leukocyte count, as well as the rapidly increasing agglutination titer of the patient's serum for *B. paratyphosus A*, would be explained satisfactorily in this way.

The case is unique in that the wall of the cyst contained a far greater amount of muscle tissue and the mucosa lining the cyst was much better developed than was found to be true in other similar cases hitherto reported.

REVIEW OF THE LITERATURE

By a careful search of the literature it has been possible to find reports or references to reports of 109 cases of cystic dilatation of the extrahepatic bile ducts. No account has been taken of cylindric enlargements such as not infrequently occur after partial or complete occlusion of the common duct by stone, tumor, traumatic stricture or pancreatitis. In a few such cases there has been cystic dilatation (Fowler,¹ Eve, Wilks-Moxon, Söderlund² and others), but these have been excluded by most previous authors, and we have not included them. The cystic dilatations associated with complete atresia of the common duct in infants have also been excluded (Witzel, Elperin, Oxley,³ Ylppö, Bohm, Buzik, Wickham-Legge, Parker and von der Werth), as have the dilatations of the hepatic and cystic ducts (Derwissieu, Rosenburg, Elisher, Oglobin,⁴ and others), although some or all of these have been included in some reviews. We think the case reported by Flechtenmacher⁵ should be excluded as one of an unproved cyst of the choledochus. In a number of reviews the case credited to Schilbe is mentioned. The only reference given is the citation by Waller, and since Waller gives no bibliographic reference it seems desirable to exclude this case. On account of its similarity to Letulle's case,⁶ we are of the opinion that it is his case

1. Fowler, R. S.: Choledochus Cyst, *Ann. Surg.* **64**:546, 1916.

2. Söderlund: A Case of Stone in the Bile Ducts, *Acta chir. Scandinav.* **59**: 253, 1925.

3. Oxley, M. G. B.: Congenital Atresia of the Duodenal Opening of the Common Bile-Duct in an Infant, Producing a Large Abdominal Tumor, *Lancet* **2**:988 (Dec. 8) 1883.

4. Oglobin, A. A.: Idiopathic Cysts of the Bile Ducts, *Vestnik khir.* **9**:177, 1927; abstr., *Internat. Abstract Surg.*, October, 1928, p. 324.

5. Flechtenmacher, C.: Operativ entfernte Choledochuszyste im Ligamentum hepato-duodenale, *Wien. klin. Wchnschr.* **32**:365, 1919.

6. Letulle, Maurice: Dilatation kystique des voies biliaires cholangiectasies congenitales, *Presse méd.* **21**:97 (Feb. 1) 1913.

under the wrong name. In several reviews, the case of Bakes,⁷ subsequently reported by Sternberg,⁸ and that of Hildebrand,⁹ later reported by Kremer,¹⁰ have been included once under each author, thus making 4 reports of 2 cases. On the other hand, we (along with others) are including the cases of Heid,¹¹ Heiliger,¹² Broca,¹³ Yamanouchi¹⁴ and Wettwer,¹⁵ all of which were excluded by S  n  que and Tailhefer.¹⁶ The best reviews have been those of Waller,¹⁷ S  n  que and Tailhefer¹⁶ and, particularly, McWhorter.¹⁸ A well studied case is that reported by Feyrter.¹⁹ Of the 82 cases that we have accepted as ones of congenital cystic dilatation of the common duct, the original reports have been read in 52, the remaining cases being taken from the reviews of previous authors, principally from the papers by Waller,¹⁷ Dreesman,²⁰ McWhorter,¹⁸ Neugebauer²¹ and S  n  que and Tailhefer.¹⁶ From the last named paper were obtained 7 reports from the Polish literature (Ejalsberg, Kulakoff, Tothfalussy, Jedlicka, Ewoyan, Winternitz and Sebek) not previously reported in English. In addition to these

7. Bakes: *Wien. klin. Wchnschr.* **20**:298, 1907.

8. Sternberg, Carl: *Cholezystostomie*, *Wien. klin. Wchnschr.* **24**:1616, 1911.

9. Hildebrand: *Geheilte Choledochuszyste*, *Deutsche med. Wchnschr.* **39**:2224 (Nov. 6) 1913.

10. Kremer, John: *Ein Fall einer durch Cholodocho-Duodenostomie dauernd geheilten echten Choledochuszyste*, *Arch. f. klin. Chir.* **113**:99, 1919.

11. Heid: *Inaugural Dissertation*; cited by McWhorter, G. L.: *Congenital Cystic Dilatation of the Common Bile Duct*, *Arch. Surg.* **8**:604 (March) 1924.

12. Heiliger: *Inaugural Dissertation*; cited by McWhorter, G. L.: *Congenital Cystic Dilatation of the Common Bile Duct*, *Arch. Surg.* **8**:604 (March) 1924.

13. Broca: *Bull. et m  m. Soc. nat. de chir.* **23**:209, 1897.

14. Yamanouchi, K.: *Ueber die cystische Dilatation des Ductus choledochus*, *Ztschr. f. Jap. Chir. Gesellsch.*, 1921, vol. 22; abstr., *Zentralorg. f. d. ges. Chir.* **16**:228, 1922; cited by Neugebauer, F.: *Beitr. z. klin. Chir.* **131**:448, 1924; cited by Judd, E. S., and Greene, E. J.: *Surg., Gynec. & Obst.* **46**:317, 1928; cited by Willis, B. C.: *Ann. Surg.* **87**:48, 1928.

15. Wettwer: *Ein Fall von kongenitalen Choledochuscyste*, *Dissertation*, G  ttingen, 1907; cited by Waller, E.: *Ann. Surg.* **66**:446, 1917.

16. S  n  que, J., and Tailhefer, A.: *Les dilatations cong  nitales du chol  doque*, *J. de chir.* **33**:154, 1929.

17. Waller, Erik: *Idiopathic Choledochus Cyst*, *Ann. Surg.* **66**:446, 1917.

18. McWhorter, G. L.: *Congenital Cystic Dilatation of the Common Bile Duct*, *Arch. Surg.* **8**:604 (March) 1924.

19. Feyrter, F.: *Ueber Fehlbildungen der extrahepatalen Gallenwege mit St  rung der normalen Hohlraumbildung (Ver  dung, Enge und cystische Erweiterung) und des normalen Gangverlaufes*, *Virchows Arch. f. path. Anat.* **271**:20, 1929.

20. Dreesman: *Beitrag zur Kenntnis der kongenitalen Anomalien der Gallenwege*, *Deutsche Ztschr. f. Chir.* **92**:401, 1908.

21. Neugebauer, F.: *Zur Kenntnis der idiopathischen Choledochuscyste*, *Beitr. z. klin. Chir.* **131**:448, 1924.

82, references to 6 other reports were obtained, all of which probably should be included, but neither the original reports nor satisfactory reviews were available (di Natale,²² Jauregui,²³ Olivecrona,²⁴ Sieber,²⁵ Stoney²⁶ and Zaczek²⁷). Including our own case, therefore, there are 83 cases available for study.

Symptomatology.—The disease occurs predominantly in females. Sixty-eight of the 83 patients were females and 14 males and in 1 case the sex was not recorded. It is a disease of children and young adults. The ages of the 69 patients when they presented themselves for treatment were as follows: from birth to 10 years, 28 cases; from 11 to 20 years, 22 cases; from 21 to 30 years, 20 cases; from 31 to 40 years, 7 cases; over 40 years, 4 cases. The oldest patient was 56, but she knew that she had had a tumor of the abdomen for thirty-six years. In many instances, jaundice, abdominal pain or tumor was present in infancy or in childhood for a short time, and then disappeared, only to recur later and cause the patient to apply for treatment. In other cases, the attacks were intermittent over a period of many years.

The three most prominent symptoms have been tumor, jaundice and pain. An abdominal tumor was present in 60 of the 83 cases, indefinite in 5, absent or not felt in 4 and not reported in 14. Jaundice was present in 60 of the patients at the time they came under observation, and had been present in 2 others previously. It was absent and had never been noticed in 7, and was not reported in 14. In 8 it was noted as slight or very slight. There was a variation from complete absence to the intense jaundice of long-standing, complete obstruction. In many cases it was intermittent or noted on more than one occasion. Pain was reported as present in 43 cases, absent in 5 and not noted in 35. It was slight in some cases, but more often was sharp and colic-like. Jaundice and pain were associated in many instances, the jaundice appearing shortly after the pain. The stools were acholic in only a small proportion of cases, in which there was deep jaundice. In 7 cases the symptoms were accentuated by pregnancy or they appeared during or just after the beginning of pregnancy (Seyffert,²⁸ Dreesman,²⁰

22. di Natale, L.: Cisti del coledoco, Arch. ital. di chir. **23**:553 (May) 1929; abstr., Brit. M. J. **2**:30 (Aug. 24) 1929.

23. Jauregui, P.: Cyst of the Common Bile Duct, Rev. de cir. **7**:536, 1928.

24. Olivecrona, H.: Infected Cyst of the Common Bile Duct, Operation, Recovery, Acta chir. Scandinav. **62**:347, 1927.

25. Sieber, F.: Large Cyst of the Bile Ducts, Zentralbl. f. Gynäk. **53**:2848, 1929.

26. Stoney, R. A.: Cyst of the Common Bile-Duct, Irish J. M. Sc., December, 1929, p. 764.

27. Zaczek: Congenital Cyst of the Common Bile-Duct, Polski Przegl. Chir. **6**:639, 1927.

28. Seyffert, cited by McWhorter (footnote 18).

Goldammer,²⁹ Hildebrand,⁹ McWhorter,¹⁸ Bachkiroff³⁰ and Zinninger and Cash). In the case reported by S  n  que and Tailhefer, the symptoms were relieved by pregnancy.

Fever was fairly frequent but not constant. It was mild in the majority of cases, and severe in only a few when definite infection of the contents of the cyst was present.

Diagnosis.—The preoperative diagnosis has usually been rather obscure, and in many instances either no definite diagnosis was made or else several were suggested. The correct diagnosis has been made before operation in only 3 cases (Iselin,³¹ Neugebauer²¹ and Taylor³²). In a fourth case, the correct diagnosis was considered, only to be rejected in favor of that of a more common condition (Wright³³). The most frequent diagnosis made has been echinococcus cyst (eighteen times). Other diagnoses in the order of frequency have been: pancreatic cyst, seven times; stone in the common duct, six times; mesenteric cyst, three times; cholecystitis, four times; enlarged gallbladder, three times; malignant growth, tuberculosis and cyst of the kidney, twice each, and retroperitoneal tumor, intestinal obstruction, ovarian cyst, catarrhal jaundice, perforation of the gallbladder and cyst of the liver, once each. In 35 cases, either no diagnosis was made or else it was not noted.

Even at operation the true condition was not recognized in a number of instances, and in nearly every one of these the termination was fatal. Five patients were treated by excision without anastomosis of the hepatic duct to the intestine, while in a number the tumors were drained as supposed echinococcus cysts, pancreatic cysts, cysts of the liver or distended gallbladders.

Pathology.—The gross appearance was much the same in all cases, and one is struck by the similarity of the observations made at operation. The large, tense, cystic tumor, generally spherical, lay in the upper part of the abdomen just below the liver and pushed the stomach downward and to the left and the duodenum downward. The position was retroperitoneal, sometimes in front of the duodenum and sometimes behind it. The gallbladder was generally found to be either small or of normal size, and sometimes was not seen at operation. In all except 2

29. Goldammer: Beitr  ge zur Chirurgie der Gallenwege, Beitr. z. klin. Chir. **55**:214, 1907.

30. Bachkiroff: Sur la pathog  nie des kystes du chol  doque, Chir. Arch. Veliaminova. **27**:63, 1911; cited by S  n  que and Tailhefer (footnote 16).

31. Iselin, Hans: Gemeinsame Cyste der Gallen-und Pankreaswege, Arch. f. klin. Chir. **145**:304, 1927.

32. Taylor, Julian: Cystic Dilatation of the Common Bile-Duct: Record of an Example, Brit. J. Surg. **16**:327, 1928.

33. Wright, H. W. S.: Congenital Diverticulum of the Common Bile Duct, Surg., Gynec. & Obst. **39**:156, 1924.

(Seeliger³⁴ and Hill and Ramsay³⁵) of the cases in which the details were noted, the cyst involved only the extraduodenal portion of the duct, and the lower intraduodenal portion varied in length from 0.7 to 4 cm. In these 2 cases, the authors believed that the dilatation involved the entire length of the duct. In 3 other instances (Iselin,³¹ Mayesima³⁶ and Matthieu³⁷), the pancreatic duct entered the cyst, so that the dilatation probably involved at least part of the intraduodenal portion. Seeliger³⁴ also thought that in his case the pancreatic duct entered the cyst, but he was not quite sure that it did so.

The cysts have varied greatly in size. The smallest was in a still-born fetus born nearly at term which was described by Heiliger;¹² the cyst measured 3 by 2.5 cm. The largest was estimated to contain 8 liters (Reel and Burrell³⁸). Twelve of the cysts for which the quantity of fluid was recorded held from 500 cc. to 1 liter; eleven, from 1 to 2 liters; seven, from 2 to 3 liters; three, from 3 to 4 liters, and four, more than 4 liters.

The wall of the cyst has varied considerably in thickness and in structure. In 9 cases it was found to be from 2 to 3 mm. in thickness; in 3, from 4 to 5 mm., and in 2 from 7 to 7.5 mm. In several cases it was described as thick, and in others as thin; in 4 cases it was described as very thin, and in 2 of these (Waller¹⁷ and Reel and Burrell³⁸) it was ruptured during the operation. The wall was generally vascular, and has been described grossly as made up of fibrous tissue which seemed to be lined by mucosa. However, in only 7 of the cases was any epithelial lining demonstrated by microscopic examination, and in no instance was the epithelium well developed. It is striking that in 24 cases it was definitely stated that in the histologic preparations no epithelium was found lining the inside of the cyst. The rapid disintegration of the epithelium that lines the larger biliary passages is well known, and it is not unreasonable to suppose that this has been a factor in the large number of instances in which no epithelium was found. All reports of microscopic examination state that the wall was largely composed of connective tissue. In 12 cases it was stated that muscle was not present, while in 9 more there was only the statement that the wall was made up of connective tissue, so that presumably muscle was absent in these cases as well.

34. Seeliger, S.: Beitrag zur Kenntnis der echten Choledochuscysten, Beitr. z. klin. Chir. **99**:158, 1916.

35. Hill, N. H., and Ramsay, R. A.: Cystic Dilatation of the Common Bile Duct, Brit. M. J. **2**:991 (Nov. 28) 1925.

36. Mayesima, J.: Zur Kasuistik der primären cystischen Erweiterung des Ductus choledochus, Deutsche Ztschr. f. Chir. **119**:338, 1912.

37. Matthieu, J.: Congenital Cyst of the Common Bile Duct, Ann. Surg. **92**:159, 1930.

38. Reel, P. J., and Burrell, N. E.: Cystic Dilatation of the Common Bile Duct, Ann. Surg. **75**:191, 1922.

At operation, the opening of the cyst into the duodenum was definitely demonstrated in only 1 case (Waller¹⁷). At autopsy a great variety of conditions has been found in the terminal portion of the duct and at the outlet of the cyst. In 17 cases, a valvelike fold was found over the outlet, and in a number of these there were similar folds over the mouths of the hepatic and cystic ducts. (McWhorter¹⁸ included the cases of Ebner³⁹ and Waller¹⁷ in this group, but we have been unable to confirm this.) The course of the duct through the duodenum was somewhat abnormal in a large number of cases. In 11, there were one or more sharp kinks, and in 13 there was narrowing or stenosis.

It is hard to arrive at a definite conclusion as to how frequently there was a complete atresia of the duct. In many cases, no opening was found between the cyst and the intestine at operation, but the clinical history and the preoperative findings precluded the assumption of complete obstruction, and in others in which no opening was found at operation, it was found later at autopsy. In the case reported by Butters,⁴⁰ there was deep jaundice, but the data are incomplete. In the case reported by Rolleston,⁴¹ only the pathologic specimen was presented, without a clinical history. In the cases reported by Seeliger,³⁴ Wyllie⁴² and Giezendanner,⁴³ an opening was not found at autopsy, even by serial sections in Giezendanner's case, but in none of these was there clinical evidence of complete obstruction. In the case reported by McWhorter,¹⁸ no opening was found at operation during excision of the cyst, but again the symptoms and signs were not those of total obstruction. In the cases reported by Hildebrand⁹ and Swain,⁴⁴ only the changes found at operation were given, but deep jaundice and acholic stools were present, so that a total occlusion of some sort must have existed. In the case reported by Lavenson,⁴⁵ there was deep jaundice with acholic stools for eight months, and at autopsy the duct was observed as a definite structure, the lumen of which was completely obliterated for a considerable distance. In a large number of cases an obstruction could not be demonstrated.

39. Ebner, A.: Idiopathische Choledochuscyste und Purpura haemorrhagica fulminans, *Beitr. z. klin. Chir.* **64**:473, 1909.

40. Butters: Choledochus-Zysten, *Deutsche med. Wchnschr.* **36**:1351 (July 14) 1910.

41. Rolleston, Humphry D.: *Diseases of the Liver, Gall-Bladder and Bile Ducts*, ed. 3, New York, The Macmillan Company, 1905, p. 651.

42. Wyllie, W. G.: Congenital Cyst of the Common Bile-Duct, *Lancet* **1**:1342, 1925.

43. Giezendanner, Ernst: Beitrag zum Studium der kongenitalen Choledochus-zysten, *Frankfurt. Ztschr. f. Path.* **38**:150, 1929.

44. Swain, W. P.: A Case of Cholecystenterostomy with the Use of Murphy's Button, *Lancet* **1**:743 (March 23) 1895.

45. Lavenson, R. S.: Cysts of the Common Bile Duct, *Am. J. M. Sc.* **137**:563, 1909.

The contents of the cyst were reported to be infected in 14 cases (Arnolds,⁴⁶ Bolle,⁴⁷ Brun and Hartman,⁴⁸ Budde,⁴⁹ Dreesman,²⁰ Iselin,³¹ Krabbel⁵⁰ (?), Letulle,⁶ Schürholz,⁵¹ Sebek,⁵² Taylor,³² Wagner,⁵³ Zipf⁵⁴ and Zinninger and Cash).

The condition of the liver was not uniformly characteristic and apparently depended on the degree of obstruction. In the cases in which there was deep jaundice, biliary cirrhosis or interstitial hepatitis was described. In 4 cases, there were areas of focal necrosis in the liver (Mayesima,³⁶ Lange,⁵⁵ Zipf⁵⁴ and Zinninger and Cash).

Treatment.—The various types of treatment and the results are summarized in table 1.

TABLE 1.—*Types of Treatment in Cases Reported in the Literature*

Treatment	Number	Died	Recovered
No treatment.....	8	8	0
Aspiration	3*	3	0
Drainage only.....	27	24†	3‡
Drainage followed by secondary anastomosis.....	14	5	9
Primary anastomosis of cyst to intestine.....	18	5	13
Excision of cyst; primary anastomosis of hepatic duct to intestine	3	1	2
Excision of cyst with drainage; secondary anastomosis to intestine	1	0	1
Excision or attempted excision of cyst, with or without drainage	6	6	0
Nature of operation not known.....	3	2§	..
Total	88	54	28

* Laparotomy was performed in one case.

† Three patients died after from one to three months of hemorrhage from fistula.

‡ One patient died after three years of pulmonary tuberculosis; 1 was well four years, and 1 was well after one and one-half years.

§ The outcome of one case was not known.

46. Arnolds: Manneskopfgrossen Retentionscyste des Choledochus, Deutsche med. Wchnschr. **32**:1804 (Nov. 1) 1906.

47. Bolle, H.: Ein Fall von idiopathischer Choledochuscyste, Deutsche med. Wchnschr. **48**:1381 (Oct. 13) 1922.

48. Brun and Hartman: Bull. et mém. Soc. nat. de chir. **23**:207, 1897.

49. Budde, Max: Ueber die Pathogenese und das Krankheitsbild der cystischen Gallergangerweiterung (sogenannte idiopathische Choledochuscyste), Deutsche Ztschr. f. Chir. **157**:364, 1920.

50. Krabbel, Max: Zum operativen Heilung der idiopathischen Choledochuscyste, Beitr. z. klin. Chir. **130**:159, 1924.

51. Schürholz: Ein Fall von sogenannten idiopathischer Choledochuscyste, Arch. f. klin. Chir. **118**:91, 1921.

52. Sebek: O pricinach ysiniku, pathologii a symptomologii tak zvané idiopathické cysty choledochu, Časop. lék. česk. **66**:1720, 1927; cited by Sèneque and Tailhefer (footnote 16).

53. Wagner, A.: Beitrag zur Chirurgie der Gallenwege, Deutsche Ztschr. f. Chir. **145**:15, 1918.

54. Zipf, Karl: Ueber idiopathische Choledochuscysten, Arch. f. klin. Chir. **122**:615, 1922.

55. Lange, Kurt: Beitrag zur idiopathischen Choledochuscyste, Zentralbl. f. Chir. **54**:2287, 1927.

Aspiration alone was performed in only 3 cases, and all of the patients died. In several instances this procedure was followed by leakage of bile into the peritoneal cavity, necessitating laparotomy. In 8 cases, because of the extreme illness of the patient, no treatment for the specific condition was given. These cases also terminated fatally.

Drainage, generally by marsupialization, was the procedure most frequently followed—in 41 cases in all. In 27 of these it was the only procedure used, and of this number only 3 patients lived more than three months. Clairmont's⁵⁶ patient died three years later of pulmonary tuberculosis, with a persistent biliary fistula, but with bile in the stools. In McConnell's⁵⁷ case, the biliary fistula opened and closed several times, and a second laparotomy was done because of loss of appetite and occasional abdominal pain; however, except for the exploration, nothing was done. The patient was reported as well four years after the first operation. In the case reported by Reel and Burrell,³⁸ the fistula closed, and the patient was reported as well a year and a half after operation.

Fourteen of the patients in whom drainage was done had a subsequent anastomosis between the cyst and the intestine. Of these, 5 died and 9 survived, but 1 (Hildebrand⁹) had to have a third operation to enlarge the stoma made at the second operation. In nearly every instance in which death occurred following the second operation, it came shortly after operation, presumably from shock. In a number of cases in which the patients were very ill, drainage alone was carried out at the first operation with the idea of performing an anastomosis when the jaundice was less intense. However, most of the patients died too soon to permit of a second operation.

In 18 cases an anastomosis of the cyst to some portion of the intestine was done at the first operation, and in 3 others a partial or complete excision of the cyst was made, with a primary anastomosis of the stump of the hepatic duct to the intestine. In the 21 cases in which a primary anastomosis was done, there were 6 deaths and 15 recoveries.

Excision of the cyst without anastomosis was done in 6 cases, all of which terminated fatally. In 1 case excision of the cyst with drainage of the hepatic ducts was carried out, followed by anastomosis of

56. Clairmont: *Zystische Dilatation des Ductus choledochus*, *Wien. klin. Wchnschr.* **24**:1616, 1911.

57. McConnell, A.: *Cyst of the Common Bile Duct*, *Brit. J. Surg.* **7**:520 (April) 1920.

TABLE 2.—Summary of Eighty-Three Cases Cited

Num- ber	Author	Year	Sex	Age	Tumor	Jaundice	Pain	Diagnosis	Treatment	Result
1	Adam, L.: Idiopathische Choledochus- cyste, Zentralbl. f. Chir. 50 : 997, 1923	1923	F	31	+	+	+	Bile cyst; pancreatic cyst	1. Drainage; 2. cholo- dochooduodenostomy 3 months later Drainage	Recovered; well 1 year later Died, 1 day after operation
2	Arnison, cited by Robson, A. W. Mayo: Diseases of the Gall Bladder and Bile Ducts, ed. 3, New York, William Wood & Company, 1904, p. 200; cited by Mc- Whorter ¹⁸	1891	?	?	+	+	?	Pancreatic cyst		
3	Arnolds ⁴⁶	1906	F	13	+	+	+	Echinococcus; a ma- lignant condition ?	Drainage	Died, 1 day after operation
4	Ashby, H.: M. Chron. 10 : 28, 1898; cited by McWhorter ¹⁸ ; cited by Rol- leston ⁴¹	1898	F	7	+	+	?		Aspiration ten times in 3 months; then an attempt to anastomose	Died, 1 day after operation
5	Ashby, H. T., and Platt, H., cited by Morley, J.: Brit. J. Surg. 10 : 413, 1923	1923	F	6½	?	+	+		1. Drainage; 2. anastomosis	Died
6	Bachkroff ³⁰	1911	F	21	+	Echinococcus cyst of liver	Attempt to resect	Died of hemorrhage
7	Bakes ⁷ and Sternberg ⁸	1907 and 1911	F	22	0	+	+	Pancreatic or mesen- teric cyst	Primary anastomosis	Recovered; died 3 years later of other causes; autopsy by Sternberg
8	Bohmanusson, C.: Cyst of the Common Bile Duct, Acta chir. Scandinav. 56 : 440, 1924	1923	M	3½	+	+	..	Retroperitoneal tumor	Primary anastomosis	Recovered
9	Bolle ⁴⁷	1922	F	13	+	Slight	++	Congestion of liver; tuberculosis; peri- tonitis; echinococcus	1. Aspiration; 2. drainage; 3. anas- tomosis; gall- bladder removed For tuberculosis	Recovered (5 weeks)
10	Broca ¹³	1897	F	10	+	Slight	..	Generalized tubercu- losis		Died
11	Brun and Hartman ⁴⁸	1897	F	3½	+	0	?	Infected echinococcus	1. Drainage; 2. anastomosis	Recovered
12	Budde ⁴⁹	1920	F	22	+	+	+		Drainage	Died
13	Butters ⁴⁰	1910	M	5	+	+	..	?		Died, several days after operation
14	Chairmont ⁵⁶	1911	M	22	+	+	..	?	Drainage	Recovery; died, 3 years later of pulmonary tuberculosis
15	Douglas ⁶⁵	1852	F	17	+	+	..	?	Aspiration	Died, 14 days after operation
16	Dreesman ⁵⁰	1906 1908	F	24	+	+	++	Echinococcus	1. Drainage; 2. anastomosis 3 months later Drainage	Died, 3 days after operation
17	Ebner ³⁹	1908	F	18	+	+	++	Echinococcus or cyst of the liver		3 months later severe purpura developed, and patient died in 4 days of hemorrhage
18	Edgeworth ⁶³	1895	F	4½	+	+	..	Enlarged gallblad- der, with partial obstruction of common duct	Drainage of gall- bladder supposedly	Died, 1 week after operation

19	Ejalsberg: cited by Sebeke ⁵²	1924	F	40	?	Excision and anastomosis	Died
20	Ewoyan ⁷¹	1925	M	6	?	Excision and drainage	Died after 3 months, of hemorrhage
21	Exner, A.: Cholelithuseyste, Wien. klin. Wchnschr. 24 : 1615, 1911	1911	F	23	..	+	Pancreatic cyst	Drainage	Died (hepatic insufficiency?)
22	Fenger: Tr. Am. S. A. 14 : 639, 1896; cited by McWhorter ¹⁸	1896	F	33	+	+	Stone in common duct	Cyst opened and closed, gallbladder drained	Died, 24 hours after operation
23	Feyrer ¹⁹	1929	F	7	Intestinal occlusion	Not treated	Died
24	Gelzandanner ¹³	1929	F	4	3½ months slowly developed	+	?	No operation	Died
25	Goldammer ²⁰	1907	F	21	+	+	Echinococcus	Excision of cyst	Died, several hours after operation
26	Heid ¹¹	1893	F	14	+	+	+	No operation	Died, of diphtheria and erysipelas
27	Heiliger ¹²	1910	M	Fetus	..	0	..	No operation	Recovered; presented 5 years later by Kremer
28	Hildebrand ⁹ and Kremer ¹⁰	1913 and 1918	F	18	+	++	Cyst in region of liver, with compression of common duct	1. Drainage; 2. anastomosis; 3. larger anastomosis	Died, 22 hours after operation
29	Hill and Ramsey ³⁵	1925	F	2	..	Had at 9 months	?	Drainage	Died, 1 month after operation, of hemorrhage from cyst
30	Ipsen ⁷⁰	1913	F	18	+	+	+	Drainage	Recovered; pancreatic fistula reopened in 1927
31	Iselin ³¹	1927 Patient seen in 1918	M	36	+	Repeated attacks	Cyst of common duct	Hepatic duct implanted into duodenum; partial excision of cyst; drainage	Cured
32	Jadlicka, cited by Sebek ⁵²	1925	F	45	?	Primary anastomosis	Recovered
33	Judd, E. S., and Greene, E. L.: Cholelithus Cyst, Surg., Gynec. & Obst. 46 : 317, 1928	1928	F	13	+	Slight	Cholecystitis with stones	Primary anastomosis; drainage of gallbladder	Died, 1 month after operation
34	Kolb ⁶²	1905	F	10	+	+	Cyst, echinococcus(?)	1. Aspiration; 2. drainage	Died, 1 month after operation
35	Konitzky ⁵⁰	1888	F	21	+	+	?	Drainage	Died, 8 days after operation, pulmonary embolus
36	Körte ⁷²	1904	F	26	..	++	+	Primary anastomosis with drainage	Died, 4 days after operation, of hemorrhage from aneurysm of hepatic artery in wall of cyst
37	Krabbel ⁵⁰	1924	F	8	+	+	Echinococcus; abscess of liver	1. Drainage; 2. anastomosis; 3. closure of fistula	Recovered

TABLE 2.—Summary of Eighty-Three Cases Cited—Continued

Num- ber	Author	Year	Sex	Age	Tumor	Jaundice	Pain	Diagnosis	Treatment	Result
38	Kulakoff, cited by Sebek ⁵²	1924	F	21	Pancreatic or mesenteric cyst ?	Drainage	Died
39	Lange ⁵³	1927	F	21	+	..	+	..	Drainage	Died, 2 days after operation
40	Lavenson ⁴⁵	1909	F	8	+	4 months	0	0	Excision	Died, 3 days after operation
41	Letulle ⁶	1913	F	25	3 weeks	1 year	0	Echinococcus	Drainage	Died, 8 days after operation
42	McConnell ⁵⁷	1919	F	11	+	+	+	?	1. Drainage; 2. drainage; 3. exploration, cyst size of walnut found, nothing done	Recovered; patient well and wound healed after 4 years
43	McWhorter ¹⁸	1924	F	49	+	+	+	Stone in common duct	Excision of cyst and gallbladder, and anastomosis of hepatic duct to duodenum	Recovered
44	Matthieu ³⁷	1930	M	6 weeks	+	++	?	?	Not treated	Died
45	Mayesina ³⁰	1912	M	2	+	+	+	?	Laparotomy; cyst aspirated; no drainage	Died, 3 months after operation
46	Melchhoff: Dilatation idiopathique du cholédoque, Russk. Klin. 3: 74, 1925; cited by Sénèque and Tailhefer ¹⁰	1925	F	32	0	+	+	Cholecystitis	1. Anastomosis to stomach; 2. gastro-enterostomy	Recovered
47	Morley, John: Congenital Cyst of the Common Bile Duct, Brit. J. Surg. 10: 413, 1923	1923	F	17	+	Once	+	Ovarian cyst	1. Drainage; 2. anastomosis 3 weeks later	Recovered
48	Moynihan, (McWhorter) Guy's Hosp. Museum No. 1419	1904	F	21	..	+	2½ years	Stenosis; valve formation; cystic duct dilated; hepatic ducts dilated	Two aspirations; operation for drainage	Died, 2 days after operation
49	Neugebauer ²¹	1924	F	21	+	+	+	Cholelithiasis	Primary anastomosis	Died, 5 days after operation
50	Nicolaysen, J.: Tumor cysticus ductus hepatici et cholédochi dilate, Zentralbl. f. Chir. 16: 1269, 1899; cited by Waller ¹⁷ ; cited by McWhorter ¹⁸	1899	F	8	+	++	Packing against cyst; drainage 6 days later	Died, 1 day after operation
51	Pummer, R.: Zur Behandlung der idiopathischen Cholelithiasis, Med. Klin. 21: 1608, 1925	1925	M	23	+	+	+	None	Primary anastomosis	Recovered
52	de Quervain: Spezielle chirurgische Diagnostik, 1922, p. 398; quoted by Glezen-danner ⁴³	1922	F	?	?	..	+	?	?	?
53	Reel and Burrell ³⁸	1922	F	56	+	36 years	+	+	Tube drainage	Well, 1½ years after operation

54	Roberts: Thèse, Lausanne, 1914; cited by McWhorter ¹⁸	1914	F	2	+	+	+	0	?	Drainage	Died, 1 week after operation
55	Rollleston ⁴¹ ; Museum specimen, New-castle-on-Tyne, no. 382-2	1905	F	9	No operation	Died
56	Rostowzew ⁵⁸	1902	F	13	+	3 years	+	..	Echinococcus cyst	Drainage	Died, 1 day after operation
57	Rotgans ⁶⁰	1913	F	5	+	0	+	+	Cholecystitis	Drainage and cholecystectomy; anastomosis 3 months later	Recovered
58	Russell ⁶⁰	1897	M	8	+	3 days	+	+	Echinococcus (catarrhal jaundice)	Drainage	Died, 4 days after operation, of hemorrhage
59	Schloessmann ⁶¹	1911	F	7	+	+	+	+	Echinococcus cyst	Aspiration (signs of leakage); drainage	Died, 6 days after operation
60	Schürholz ⁶¹	1921	F	3	+	+	+	+	Echinococcus	1. Drainage; 2. anastomosis 6 weeks later	Died, 3 hours after operation
61	Sebek ⁶²	1927	F	18	+	+	+	+	Stone in common duct	1. Excision and drainage; 2. anastomosis	Recovered
62	Seeliger ³⁴	1916	F	13	+	+	+	+	Echinococcus; perforated gallbladder (?)	1. Drainage, delayed 3 days; 2. opening into duodenum made	Died, 6 days after operation
63	Sénèque and Tailhefer ¹⁶	1929	F	32	+	+	+	+	Cholecystitis	Primary anastomosis	Recovered
64	Seyffert ²⁸	1888	F	23	+	1 year	+	+	Pancreatic cyst	Drainage	Died, 1 month after operation, of hemorrhage
65	Snit: Et tilfælde af idiopathisk chole-dochuyste, Medicinsk Rev. 32: 285, 1915; cited by Waller ¹⁷	1915	F	17	+	+	0	+	Cyst in liver	Excision	Died, 8 days after operation
66	Swain ⁴⁴	1895	F	17	+	+	+	0	Enlarged gallbladder	1. Aspiration; 2. button for intestinal anastomosis	Recovered
67	Taylor ³²	1928	F	23	+	+	+	+	Cystic dilatation of common duct	Anastomosis to stomach	Recovered
68	Tothfalussy, cited by Sebek ⁶²	1925	M	12	Excision and drainage	Died
69	Wagner ⁵³	1918	F	47	+	+	+	+	Malignant condition of gallbladder or liver; stone in common duct	Button for intestinal anastomosis	Died, 4 days after operation

TABLE 2.—Summary of Eighty-Three Cases Cited—Continued

Num- ber	Author	Year	Sex	Age	Tumor	Jaundice	Pain	Diagnosis	Treatment	Result
70	Waller ¹⁷	1917	F	10	+	0	+ began at age of 3	Indeterminate	Primary anastomosis	Recovered
71	Walzel, P.: Idiopathische Cholelith- cyste, Zentralbl. f. Chir. 48: 594, 1921	1921	F	27	?	1. Excision of gall- bladder and cyst— hepatic duct drained to surface; 2. anas- tomosis of hepatic duct to stomach; two subsequent operations	Hemorrhage; died
72	Weiss ⁶⁴	1909	M	6	+ 7 months	+ Slight, inter- mittent	+	Echinococcus	1. Diagnostic punc- ture; 2. exposure and suture; 3. drainage None	Died, ninth day after operation
73	Weltwer ¹⁵	1905	F	15	+	Inter- mittent 8 years	?	?		Died
74	Willis ⁶⁶	1928	M	12	+	0	6 months	Empyema or hydrops of gallbladder	Primary anastomosis	Recovered
75	Wilson ⁶⁷	1930	F	14	+	0	+	None reported	Primary anastomosis	Recovered
76	Winternitz, cited by Sebek ⁵²	1926	F	26		Primary anastomosis	Recovered
77	Wright ³³	1924	M	15	+	+ 5 months	Slight	Cyst of common duct (?); rejected; stone in common duct	Primary anastomosis	Died, 3 days after operation, of cholelithia (?)
78	Wyllie ¹²	1925	F	6	+ 1 year	+ 1 year, inter- mittent	?	?	Drainage; anastomosis	Died, 48 hours after operation
79	Yamanouchi ¹¹	1921	F	4	None	Operation	Died
80	Yamanouchi ¹¹	1921	F	16	None	Operation	Died
81	Zimmer, Hans: Idiopathische Chole- lithocyst, Zentralbl. f. Chir. 51: 424, 1924	1924	F	22	+ 1 month	De- veloped grad- ually	+	Pancreatic cyst; echinococcus; mesenteric cyst; cyst of kidney	1. Drainage; 2. anastomosis 1 month later	Recovered
82	Zipf ⁵⁴	1922	F	14	+	Slight	+ 3 days		Drainage	Died, 3 days after operation
83	Authors' case.....	1930	F	40	Indef- inite	0	+ 4 to 5 years; acute 1 month	Hydrops of gallbladder	Primary anastomosis	Died, 12 days after operation of acidosis

the stump of the hepatic duct to the intestine at a second operation. This patient recovered.

The total mortality in the 83 cases was 65 per cent (54 cases). In the cases in which the patients were not treated, in those in which they were treated by aspiration alone and in those in which they were treated by excision alone, the mortality was 100 per cent. In the 27 cases in which the patients were treated by drainage alone, the mortality was 88 per cent. In the 14 cases in which a secondary anastomosis was done, the mortality was 35 per cent; in the 21 in which a primary anastomosis was made, it was 28.9 per cent.

From these results one may conclude that internal drainage should be done in all cases and that anastomosis at the primary operation apparently gives better results and a lower mortality than at a second operation. This is striking if one also considers the high mortality in the cases in which the patients were treated by drainage alone, as only those who survived that operation for some time were available for secondary operations. It is unfortunate that the late end-results are known in only a few cases. The other striking feature is the fact that failure to recognize the true nature of the condition at operation has been an important factor in the high mortality. From an anatomic and physiologic point of view, it would seem that excision of the cyst with anastomosis of the hepatic duct to the intestine should be the method of choice, but unfortunately this procedure is rarely feasible for two reasons. In the first place, in deeply jaundiced patients such an operation would probably lead to fatal hemorrhage, and in the second place, the cysts usually arise directly beneath the liver, so that no extrahepatic portion of the hepatic duct is available for anastomosis.

Etiology.—The cause of cystic dilatation of the common bile duct remains obscure, though most authors think that a congenital factor is present. Various authors considered the following causes as productive of the condition:

1. Congenital malformation (Giezendanner,⁴³ Heiliger,¹² Krabbel,⁵⁰ Schürholz⁵¹ and Seeliger³⁴). In this connection, the case reported by Heiliger¹² has been repeatedly cited, in which the cystic dilatation was present in a stillborn fetus, born nearly at term. There was no jaundice; bile was present in the intestine, and the common duct below the dilatation was patent though considerably narrowed. Several other congenital abnormalities were present. The onset in childhood and the occurrence of symptoms early in life, or intermittently after beginning at an early age, are evidences in favor of a congenital origin. Giezendanner⁴³ cited many cases of frankly congenital atresia of the common duct associated with small, moderate or large cystic dilatation of the duct. In the case here reported, the thick wall of the cyst with well

developed muscle and the absence of clinical signs of obstruction are points in favor of a congenital origin. In many cases, an anatomic obstruction could not be demonstrated, and in those in which obstruction could be shown, owing to kink, valve or stenosis, the dilatation above was spherical instead of the usual cylindric dilatation observed in partial or complete obstruction due to stone, tumor or traumatic stricture. Furthermore, in spite of normal walls, the gallbladders were seldom enlarged or distended, as one would expect in ordinary obstruction, and though the hepatic ducts were described as dilated in about half the cases, the dilatation was never commensurate with that of the common duct. Valvelike folds over the mouths of the cystic and hepatic ducts may have been factors in preventing the dilatation of these structures.

2. Abnormal course of the common duct or angular insertion into the duodenum, congenital in origin, which causes kinking and obstruction (Rostowzew,⁵⁸ Arnolds,⁴⁶ Konitsky,⁵⁹ Ebner,³⁹ Russell⁶⁰ and Schloessmann⁶¹). Lavenson⁴⁵ was the first to point out that this change might be a result rather than a cause of the dilatation. Others agree with this conception, according to which the progressive enlargement pushes forward or backward, and this displacement gives rise to the abnormal course. Kolb⁶² and Dreesman²⁰ pointed out that the condition is unlike hydronephrosis, to which it has been compared, since in the latter the ureter normally begins as a relatively large cavity, while the common duct arises by the confluence of several small ducts and is normally of uniform caliber throughout. Furthermore, it is unlike hydronephrosis in that there is not uniform dilatation of the entire system above the obstruction (Heiliger¹²). In his article, Schloessmann⁶¹ stated that in the majority of the cases reported (1911) an abnormality of the insertion into the duodenum was present.

3. A valvelike fold of tissue over the mouth of the intraduodenal portion of the duct (Bakes,⁷ Sternberg,⁸ Clairmont,⁵⁶ Neugebauer²¹ and Rostowzew⁵⁸). The formation of the valve was described in 17 cases. As pointed out by Lavenson,⁴⁵ Schloessmann⁶¹ and others,

58. Rostowzew, M. J.: Ein Fall von hochgradiger cystischer Erweiterung des Ductus choledochus, *Deutsche med. Wchnschr.* **28**:739 (Oct. 9) 1902.

59. Konitsky: Inaugural Dissertation; cited by Waller (footnote 17); cited by McWhorter (footnote 18).

60. Russell, R. H.: Case of Cystic Dilatation of the Common Bile Duct in a Child, *Ann. Surg.* **26**:692, 1897.

61. Schloessmann: Beitrag zur Kenntnis der Choledochuscysten, *Deutsche Ztschr. f. Chir.* **109**:160, 1911.

62. Kolb: Inaugural Dissertation; cited by Waller (footnote 17); cited by McWhorter (footnote 18).

it is hard to imagine how a valvelike fold could occur spontaneously in a cylindric structure and cause its dilatation into a cavity. Once a cavity is present, it can easily be seen that a valvelike fold might develop, as a result of sagging at the junction of the cavity with a smaller tube draining from it. The fact that such folds were present over the mouths of the hepatic and cystic ducts in many of the specimens is in favor of such an explanation. Once a valve has formed, it can be seen how it might function to cause further enlargement and obstructive symptoms. That valvular action is often present has been demonstrated in a number of cases by the presence of intermittent jaundice and pain and by fluctuations in the size of the tumor under observation.

4. Congenital narrowing of the intraduodenal portion of the duct (Heid¹¹) or stenosis due to infection (Edgeworth⁶³).

5. Congenital weakness of the wall of the duct. This condition was first suggested as a cause by Dreesman²⁰ (1908), and later by Laven-son,⁴⁵ Mayesima,³⁶ Neugebauer,²¹ Kolb,⁶² Weiss,⁶⁴ Bolle⁴⁷ and Russell.⁶⁰ Several of these authors assumed an additional factor, such as partial stenosis or occlusion due to catarrhal inflammation, spasm or edema. This whole assumption, like most of the explanations that have been offered, is not easily capable of proof. In his case, Mayesima³⁶ said of it, that "no other cause was present." In the cases reported in which measurements of the thickness of the wall were given, the thinnest was 2 mm.; the thickest, 7.5 mm. In many cases the wall was described as thin but tough; in only 4 was it very thin, and in 2 of these it ruptured during operative manipulation; in a few cases it was described as thick. Neugebauer²¹ compared the dilatation to that of the colon in Hirschsprung's disease.

6. A complication of pregnancy. In 8 cases the symptoms bore a more or less direct relationship to pregnancy. Goldammer²⁹ thought that pressure from the enlarging uterus might have been a factor in his case. McWhorter¹⁸ expressed the belief that delivery may cause a kink in the common duct due to the release of intra-abdominal pressure.

7. Primarily congenital, but with one or more of several possible modifying factors, such as infection, spasm, kink, the formation of valves or partial atresia, which cause further development of the condition (Zipf⁵⁴).

8. Trauma. This possible etiologic factor was mentioned by Kremer.¹⁰ In the case reported by him and by Hildebrand, the patient

63. Edgeworth, F. H.: A Case of Dilatation of the Common Bile-Duct Simulating Distension of the Gall-Bladder, *Lancet* 1:1180 (May 11) 1895.

64. Weiss, S.: Ein seltener Fall von cystischen Erweiterung des Ductus choledochus, *Berl. klin. Wchnschr.* 46:1843, 1909.

had a fall at the age of 7 or 8 years. At that time the abdomen was injured, and the patient herself considered that this was the cause of the symptoms.

9. Pancreatic adenomas. In his case, Budde⁴⁹ found a minute diverticulum of the ampulla of Vater and areas of fibro-adenoma in the wall of the cyst, which he demonstrated by serial section to be continuous with the pancreas. He described these areas as pancreatic adenomas. He believed that just as diverticulae of the duodenum are present in association with aberrant pancreatic tissue, so cystic dilations or diverticulae of the common duct might be conditioned by pancreatic adenomas. In none of the other cases was fibro-adenoma found, although Reel and Burrell³⁸ found a few structures resembling bile ducts in the wall of the cyst in their case. They interpreted these structures as remnants of tissue of the liver and thought that the cyst might be of hepatic origin.

10. Pressure on the common duct by enlarged tuberculous mesenteric glands. This condition was suggested by Douglas.⁶⁵

From a glance at the foregoing paragraphs it is readily seen that most authors regarded the condition as a congenital anomaly, though many others described it as idiopathic. In 4 cases in which an abdominal operation had been carried out at some time previous to the development of symptoms, the presence of the cyst was not discovered at the first operation (in the cases of Willis,⁶⁶ McWhorter,¹⁸ Wilson⁶⁷ and S  n  que and Tailhefer¹⁶), but this does not necessarily mean that a cyst was not present at that time, as in each instance the first operation was performed on the lower part of the abdomen.⁶⁸

SUMMARY

The clinical features and the pathologic changes in a case of congenital cystic dilatation of the common bile duct are reported. Eighty-two other cases reported in the literature are reviewed. The salient diagnostic features of the condition are that it occurs much more frequently in females than in males and principally in children and young adults. The three most prominent symptoms and signs are pain,

65. Douglas: *Monthly J. M. Sc. (London)* **14**:97, 1852; cited by McWhorter (footnote 18); cited by Dreesman (footnote 20).

66. Willis, B. C.: *Congenital Cystic Dilatation of the Common Bile-Duct*, *Ann. Surg.* **87**:48, 1928.

67. Wilson, H. V., Jr.: *Choledochus Cyst*, *J. A. M. A.* **95**:399 (Aug. 9) 1930.

68. In the case of Oglobin, not included in the present series, a young man, aged 23, was operated on for high fever, severe pain, jaundice and acholic stools of sudden onset. Nothing abnormal was found. At a second operation, undertaken for recurrence of the symptoms, a large cyst filled with clear fluid was drained. At postmortem examination, a huge cystic dilatation of the common and hepatic ducts was found.

jaundice and the presence of a tumor in the right upper quadrant of the abdomen. These changes are often intermittent over a considerable period of time. The etiology is not known, but it is generally agreed that the condition is congenital.

From the point of view of treatment, it seems advisable on theoretical grounds to establish as early as possible an adequate communication between the biliary tract and the intestine, for usually there is a hindrance to outflow, whether from a kink, valve, fold, partial occlusion, or complete atresia. A second desideratum seems to be avoidance of infection of the biliary system, which frequently occurs after its anastomosis with the intestine. As a measure against infection, excision or partial excision of the cyst to reduce stasis to a minimum would appear to be the most ideal procedure. Unfortunately, on account of technical details previously mentioned, this step is usually impossible. It must also be remembered that an adequate stoma is essential, for in one case (Hildebrand⁶⁹) the first stoma made subsequently had to be enlarged, and in another case (Rotgans⁶⁹) there were recurrent attacks of pain, probably due to the small stoma. On physiologic and theoretical grounds, primary anastomosis seems to be the most desirable procedure, and, in fact, it has given the best results. The condition of the patient in the late stages of complete obstructive jaundice may preclude such a procedure, so that drainage alone may be feasible. In point of fact, in cases in which the patients survived drainage long enough to permit anastomosis, the results were comparable to those in which primary anastomosis was done; on the other hand, the patients in more than half of the cases in which drainage was done died before the second stage could be carried out, and often soon after operation—from one to several days. Frequently the cause of death was hemorrhage from the fistulas in the cases reported by Ebner,³⁹ Ipsen,⁷⁰ Russell,⁶⁰ Seyffert,²⁸ Ewoyan⁷¹ and Körte.⁷²

The most encouraging finding brought out by the cases recorded in the literature is that, on the whole, the treatment adopted in the more recent cases has been better than that used in the earlier ones. The diagnosis should not be difficult if one bears in mind that congenital cystic dilatation of the common bile duct may exist, for the clinical symptoms and the physical findings are fairly characteristic. It is to be hoped, therefore, that in the future a correct preoperative diagnosis may be made more frequently, and that there will be still further improvement in the treatment and results.

69. Rotgans, cited by McWhorter (footnote 18).

70. Ipsen, J.: *Et tilfælde af choledochuscyste*, Hospitalstid. **45**:1342, 1913; cited by Waller (footnote 17).

71. Ewoyan, cited by Sebek (footnote 52).

72. Körte: *Die Erkrankungen der Gallenwege*, Med. Praxis, 1928, p. 117; cited by Sènèque and Tailhefer (footnote 16).

CONCRETIO CORDIS

I. A CLINICAL STUDY, WITH OBSERVATIONS ON THE VENOUS PRESSURE AND CARDIAC OUTPUT *

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Disease, especially when chronic, rarely produces a single or simple change in structure or in function. Physiologic measurements of various sorts that reveal deviation from the normal when applied to patients must therefore be interpreted with caution, for it is not always easy to decide which of the mechanical or chemical changes present is responsible for the abnormal finding. From time to time, however, disease performs a simple experiment, producing a few recognizable alterations in, for example, the dynamics of the circulation: when this occurs, opportunities for study may arise that are not easily created by deliberate intention. Such an opportunity was offered by the following case.

CASE 1.—*History*.—A printer, 36 years old, white, entered Vanderbilt University Hospital through the outpatient department on Feb. 16, 1930, with the complaints of shortness of breath and generalized swelling of the body.

Previous to the onset of the present illness, the patient's health had been excellent. In childhood, he had had chickenpox, measles and whooping cough. In 1920 he had had acute gonorrheal urethritis. No history suggestive of rheumatic fever, tonsillitis, syphilis or tuberculosis could be obtained. He had had no operations.

His personal habits were good, except for the use of moderate amounts of alcoholic beverages until eight months prior to his admission to the hospital.

The patient's father died at the age of 72 of unknown immediate cause; he had suffered from cardiac and renal disease previous to this last illness. The mother died of pneumonia at the age of 67.

The onset of the present illness was six months previous to the patient's admission to the hospital. At that time he suffered repeated attacks of nausea following his usual light breakfast, but he did not vomit. The nausea was associated with attacks of cramping pain in the epigastrium lasting from thirty minutes to four or five hours, and always localized. These attacks did not occur at any other time during the day and ceased to occur after one month. Five months before admission, swelling of the feet and ankles was noticed for the first time. This would appear during the day and disappear during the night. At this time, following exposure to cold weather, the patient contracted a severe cold associated with cough and pain in the right side of his chest. Thick sputum was occasionally

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coughed up, and this contained a small amount of dark blood. An examination of the lungs was made by x-rays, and the patient was told that he had a lesion in the right lung. Four and a half months before admission to the hospital, he experienced dyspnea on exertion, and about the same time he began to have attacks soon after going to bed of what he described as "smothering spells" which were relieved by sitting up. They did not occur after he got well asleep. Three months after admission the swelling of the legs became persistent, and one month later enlargement of the abdomen was noticed and also some swelling of the face, especially of the eyelids. From November 30 to January 4, the patient was treated in a hospital by rest and the administration of digitalis and showed marked symptomatic improvement, losing most of the edema. Within twelve days following discharge from the hospital, however, edema had recurred and had become worse than it had ever been. It was at this time that he was admitted to the Vanderbilt University Hospital.

Examination.—The patient was a cooperative, intelligent, well nourished white man of 36. He appeared definitely orthopneic. Respirations were shallow. The skin was slightly cyanotic. There was evidence of a generalized edema involving the chest, abdomen, back and legs, more marked in the dependent parts of the body. The cervical veins appeared greatly distended. They did not display diastolic collapse.

Examination of the head and neck showed no other abnormalities. The chest appeared broad and symmetrical, but expansion was limited. There were signs of free fluid in both pleural cavities, rising high in the axilla on the right and to the angle of the scapula on the left. A few moist râles were heard just above the level of the fluid, but the lungs were elsewhere clear. There was no "Broadbent's sign."

The cardiac impulse was barely palpable even with the patient in the left lateral position. The only visible impulse was in the third interspace 8 cm. to the left of the midsternal line. The heart did not seem enlarged to percussion. The sounds were distant. No murmurs or friction rub could be heard. The rhythm was regular, and the rate was 110. There was no demonstrable shift in position of the heart with change in position of the body. The radial pulse was small, but not quick, and was a typical paradoxical pulse with disappearance of the impulse during inspiration. The blood pressure was 118 systolic and 104 diastolic.

The abdominal wall was edematous. There was an easily demonstrable fluid wave in the moderately distended abdomen. The liver extended 8 cm. below the right costal margin. The spleen was not palpable. The results of abdominal examination were otherwise negative.

Examination of the extremities revealed nothing abnormal, except edema of the legs and thighs sufficient to exhibit deep pitting on pressure.

For the first two and a half weeks in the hospital, there was a daily rise in temperature to a point that never exceeded 101 F. and that averaged 100 F. The temperature was normal in the mornings. During the last ten days it ranged from 97 F. to 98.8 F.

The pulse rate remained elevated throughout the period of observation, ranging from 90 to 110 beats per minute. Otherwise the physical examination revealed no abnormalities.

Urinalysis revealed: a specific gravity varying from 1.010 to 1.020; an acid reaction; a slight trace of albumin, which disappeared when diuresis took place; very few cellular and granular casts and an occasional erythrocyte or leukocyte in a centrifugated specimen.

Results of the study of the blood were as follows: erythrocytes, 4,900,000; hemoglobin, 95 per cent; leukocytes, 6,000; differential count, normal; Wassermann reaction, negative; nonprotein nitrogen, 28 mg. per hundred cubic centimeters; blood sugar, 71.4 mg.; creatinine, 1 mg., and serum protein, 7.6 Gm.

A phenolsulphonphthalein renal test (with intravenous administration of dye) showed an excretion of 40 per cent of the dye during the first hour and 10 per cent during the second.

The results of fluoroscopy of the chest and of a roentgenogram of the heart taken at 7 feet (fig. 1) were reported as follows: "There is slight enlargement of the cardiac shadow to the right. It is very difficult to make out any pulsations. The outline of the heart is sharply defined, and there is apparently some pericardial effusion. The greatest diameter of the arch is 8.4 cm. The heart's shadow

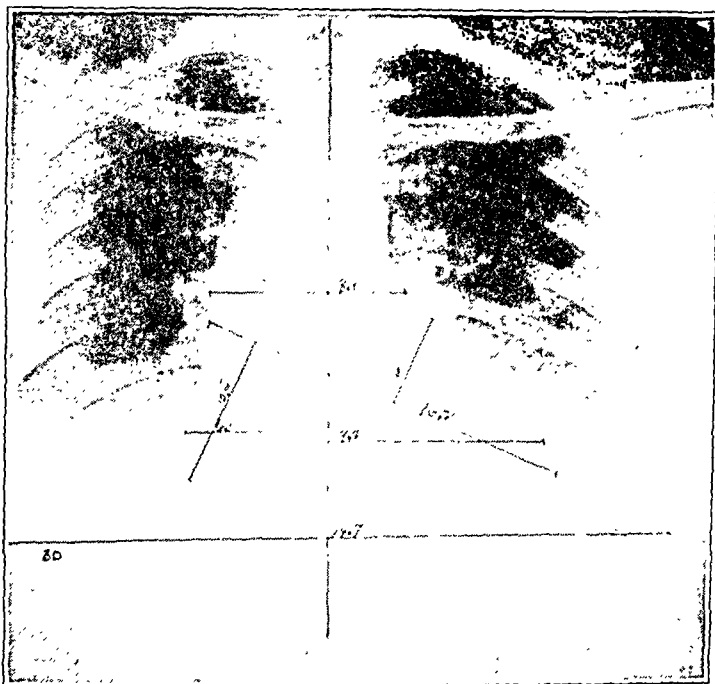


Fig. 1 (case 1).—Roentgenogram of the chest on Jan. 20, 1930, taken at a distance of 7 feet.

extends 9.2 cm. to the left and 6.1 to the right of the midline. The longest diameter of the heart is 16.2 cm. The greatest diameter of the base is 10.5 cm. The greatest diameter of the chest is 30 cm.; the distance from the midline to the left thoracic wall is 14.7 cm."

An electrocardiogram (fig. 2) showed: rate 100; P-R interval 0.16 second; inverted T waves in leads II and III; small complexes in all leads. Tracings made with the patient in different positions showed no shift of the electrical axis.

Diagnosis.—This patient exhibited many signs and suffered from many symptoms that are commonly found in patients suffering from chronic heart disease with congestive failure. It may be said that the evidences of peripheral congestion were clearer than the evidences of disease of the heart. Although there was little evidence of pulmonary edema, the patient showed marked distention of the visible veins, engorgement of the liver, peripheral edema and signs of fluid in the pleural and peritoneal cavities. The heart itself, however, showed few of the

abnormalities usually associated with congestive failure of this degree. It was but slightly enlarged, and its activity was not palpable; the sounds, far from being loud and tumultuous, were distant and weak; the pulmonic second sound was even less loud than the aortic second sound; no murmurs were heard; the systemic blood pressure and the pulse pressure were low, and the radial pulse

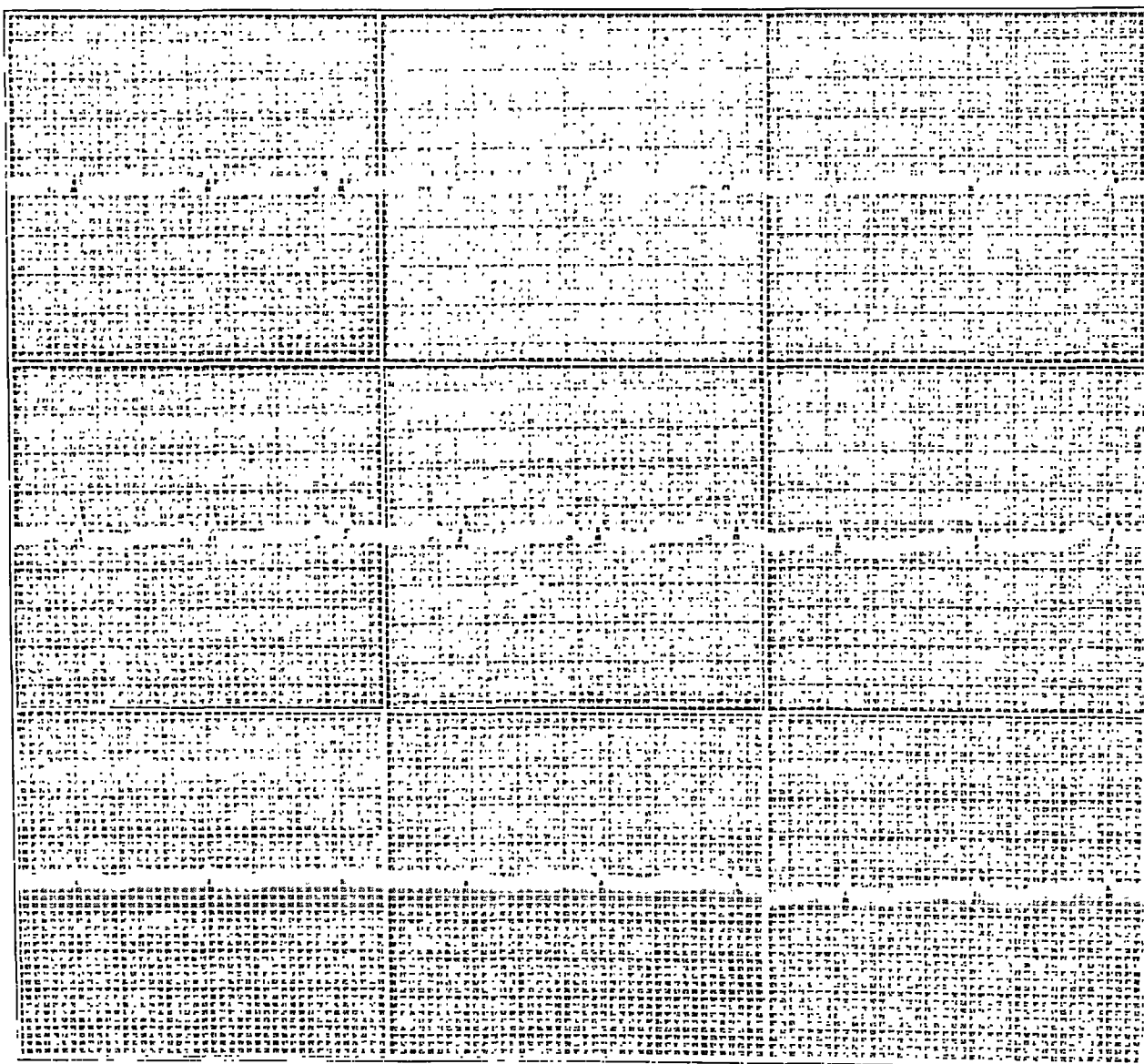


Fig. 2 (case 1).—Electrocardiographic tracings on Jan. 17, 1930, showing low voltage and slurring of QRS complexes with no shift of the electrical axis on change of position. Leads I, II and III are arranged from above downward. The horizontal columns represent dorsal, right lateral and left lateral position, respectively.

was regular, small and paradoxical. The patient thus exhibited in high degree the signs of back pressure from the right ventricle of the sort associated with failure of that ventricle. There was, however, no evidence of hypertrophy of the

right ventricle nor of any valvular or pulmonary disease to account for its failure. Moreover, the cardiac impulse was neither seen nor felt; both the cardiac dullness and the electrical axis failed to shift with change in the position of the patient, and no movement of the border of the heart was seen under the fluoroscope. Accordingly, a tentative diagnosis of adhesive pericarditis was made, of the type described by Volhard and Schmieden¹ as *concretio cordis*.

Following the arrival at the diagnosis of *concretio cordis* certain physiologic studies were projected and carried out in order to establish further the exactitude of the diagnosis, to control the treatment, and to study the mechanism of the production of symptoms. Before we embarked on these observations the patient was made much more comfortable by simple therapeutic procedures directed toward the removal of fluid. On the day of admission 1,000 cc. of fluid was removed from each side of the chest by thoracentesis, with immediate relief of the

TABLE 1.—*Determinations of the Cardiac Output of the Patient in Case 1 in the Basal, Resting Condition*

Date, 1930	Surface Area, Sq. M.	Basal Metabolic Rate, per Cent	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference, per Cent by Volume	Cardiac Output				Pulse Rate per Minute	Respirations per Min.	Blood Pressure, Mm. Hg	Pulse Pressure, Mm. Hg
					Per Minute, Liters	Per Sq. M. of Surface Area, Liters	Per 100 Cc. of Oxygen Consumed, Liters	Per Beat, Cc.				
February 1	1.71	+ 4	270	10.15	2.66	1.55	0.985	25.6	104	20	98/85	13
February 2	1.71	+ 1	246	9.04	2.72	1.59	1.10	25.6	106	22	98/86	12
February 3	1.71	0	233	11.8	1.98	1.16	0.85	18.0	110	20	96/82	14
February 5	1.71	-12	210	9.16	2.29	1.34	1.08	22.0	104	19	92/80	12
Average	1.71	- 2	240	10.04	2.41	1.41	1.00	22.8	106	20	96/83	13

orthopnea. In the succeeding three days 2,200 cc. more was removed from the right pleural cavity. Salyrgan administered intravenously, and theophylline by mouth, produced abundant diuresis. Digitalis was not given at this time. Two weeks after entry the patient had lost 7.2 Kg. and had no orthopnea, no dyspnea at rest and no edema. Furthermore, as soon as the fluid was removed from the pleural cavities it was evident that the lungs were not involved in the edema that marked the periphery. On February 1, there were no râles in the lungs, the vital capacity was 3,000 cc. (80 per cent of normal), and the oxygen saturation of the arterial blood was 98 per cent. On this evidence it was felt that diffusion in the lungs was sufficiently near to normal for studies of the cardiac output to be undertaken. These studies were carried out by the acetylene method of Grollman.² First, four determinations were made under "standard basal" conditions. The results of the studies are recorded in table 1. The determination of the cardiac output by the method of Grollman gives results that vary somewhat from those obtained by other methods. Therefore, in table 2, for convenience in comparison,

1. Volhard and Schmieden: Ueber Erkennung und Behandlung der Umklammerung des Herzens durch schwierige Perikarditis, *Klin. Wchnschr.* 2:5, 1923.

2. Grollman, A.: The Determination of the Cardiac Output of Man by the Use of Acetylene, *Am. J. Physiol.* 88:432, 1929.

we summarized the results of Grollman's³ studies of normal persons and added also the results of studies made by us on a small series of normal persons, using their method. Certain of the figures are compared graphically in figure 3.

Scrutiny of these data shows definite departure from the normal on the part of the patient. His cardiac rate, in spite of careful attention to the details of the "standard basal" conditions, never fell below 104 and averaged 106. The total

TABLE 2.—*Comparison of the Averages of the Determinations of the Cardiac Output of Forty Normal Subjects in Grollman's Series and of Five Normal Subjects in Our Series*

	Surface Area, Sq. M.	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference, per Cent by Volume	Cardiac Output			Pulse Rate per Minute	Pulse Pressure, Mm. Hg
				Per Minute, Liters	Per Sq. M. of Surface Area, Liters	Per 100 Cc. of Oxygen Consumed, Liters		
Average of Grollman's series of 40 normal subjects.....	1.76	230	5.93	3.88	2.21	1.68	60	38
Average of our series of 5 normal subjects.....	1.98	241	6.38	3.78	1.91	1.56	58	32

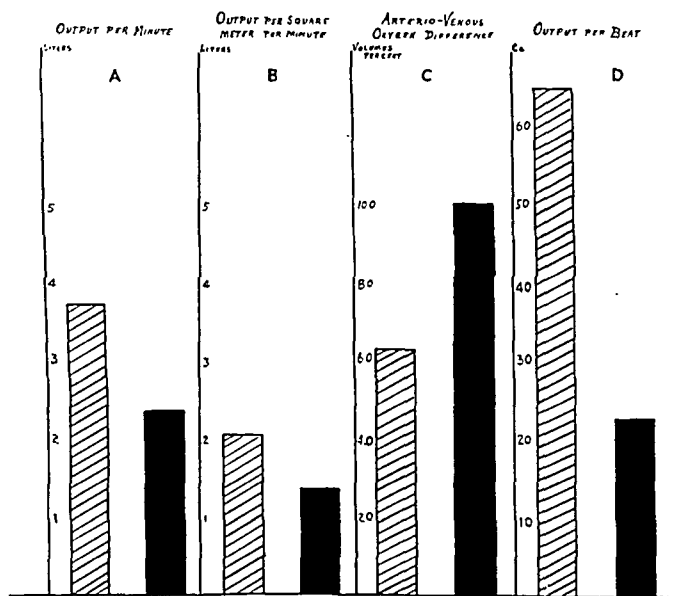


Fig. 3 (case 1).—Graphic comparison of the results of determinations of the cardiac output per minute (A), the cardiac output per square meter (B), the arteriovenous oxygen difference (C) and the cardiac output per beat (D) of a normal control subject (shaded columns) and of the patient (solid columns).

consumption of oxygen was not abnormal, but the oxygen taken out of each liter of blood as it passed through the body reached the high average of 101 cc.

3. Grollman, A.: Physiological Variations in the Cardiac Output of Man: VI. The Value of the Cardiac Output of the Normal Individual in the Basal Resting Condition, *Am. J. Physiol.* 90:210, 1929.

(10.1 per cent by volume), as compared with average normal figures of 59 and 64 cc. The cardiac output per minute was lower than in any normal person studied and 36 per cent lower than the average reported by Grollman.² The validity of the difference is shown by the fact that it holds also for the cardiac output per square meter of surface area and per hundred cubic centimeters of oxygen absorbed.

The greatest and most significant difference between this patient and normal persons is seen in the figures for the output of his heart per beat. The output per beat of normal resting persons varies between 55 and 80 cc. and averages about 65 cc. The output per beat of the patient varied between 18 and 26 cc. This finding is to be correlated with the low pulse pressures that were recorded on the occasion of each observation.

The venous pressure in *concretio cordis* was measured by Volhard and Schmieden and found to be increased to as much as 300 mm. of water. During the progress of our studies, determinations were made of the venous pressure by the method of Moritz and von Tabora.⁴ With the needle in the right basilic vein, the venous pressure measured 240 mm. of water. During gentle flexion and extension of the left arm, the venous pressure rose steadily. When the arm was again at rest, the pressure fell slowly to its previous level of 240 mm.

When the identical method was applied to a normal person, his resting pressure was found to be 70 mm. Flexion and extension of the left arm had no effect on the level of pressure in the vein of the right antecubital space.

The evidence to this point indicated a backing up from the right side of the heart due either to obstruction in the great veins or to a fibrous coat around the heart sufficiently thick and tight to prevent a proper diastolic relaxation and filling. The appearance of the heart in the fluoroscope was in favor of the latter view. It was felt that a decisive test would be the response of the heart to exercise. If the fibrous envelop assumed to be surrounding the heart was present, it was to be expected that the output of the heart per beat could not increase in response to demand for an increased circulation. Accordingly the output of the heart per minute and per beat was determined during exercise sufficient to increase the consumption of oxygen from an average of 240 cc. when the patient was at rest to an average of 535 cc. per minute. For purposes of comparison, similar observations were made on a normal young man. The observations made during exercise are summarized in table 3 and compared graphically in figure 4.

It is seen that in the normal man both the pulse rate and the heart's output per beat were increased. The cardiac output per minute was thus increased about as much as the consumption of oxygen. The utilization of oxygen remained about the same, indicating that the oxygen tension in the tissues was not greatly altered. The normal subject felt no fatigue and no dyspnea. In the patient, the circulatory response to exercise was quite different. His pulse rate, already 106, increased to 144, but the output per beat remained almost exactly at the level that was observed when he was resting. The total cardiac output per minute increased much less than the consumption of oxygen. The utilization of oxygen rose to 130 cc. per liter (77 per cent of the total oxygen capacity); the oxygen tension of the

4. Moritz, F., and von Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* 98:425, 1910.

TABLE 3.—*Determination of Cardiac Output Under Basal Conditions and Following Exercise on a Normal Control Subject and on a Patient with Concretio Cordis (Case 1)*

	Surface Area, Sq. M.	Basal Metabolic Rate, per Cent	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference, per Cent by Volume	Cardiac Output				Pulse Rate per Minute	Respirations per Min.	Blood Pressure, Mm. Hg	Pulse Pressure, Mm. Hg
					Per Minute, Liters	Per Sq. M. of Surface Area, Liters	Per 100 Cc. of Oxygen Consumed, Liters	Per Beat, Cc.				
Normal control under basal conditions....	1.84	— 7	234	6.83	3.42	1.87	1.46	50	69	11	90/62	32
Normal control after exercise	1.84	+178	683	7.12	9.60	5.22	1.40	80	120	24	125/85	40
Patient under basal conditions (av. of 4 determinations).....	1.71	— 2	240	10.04	2.41	1.41	1.00	23	106	20	96/83	13
Patient after exercise.....	1.71	+140	535	13.00	4.12	2.41	0.77	29	144	38	100/88	12

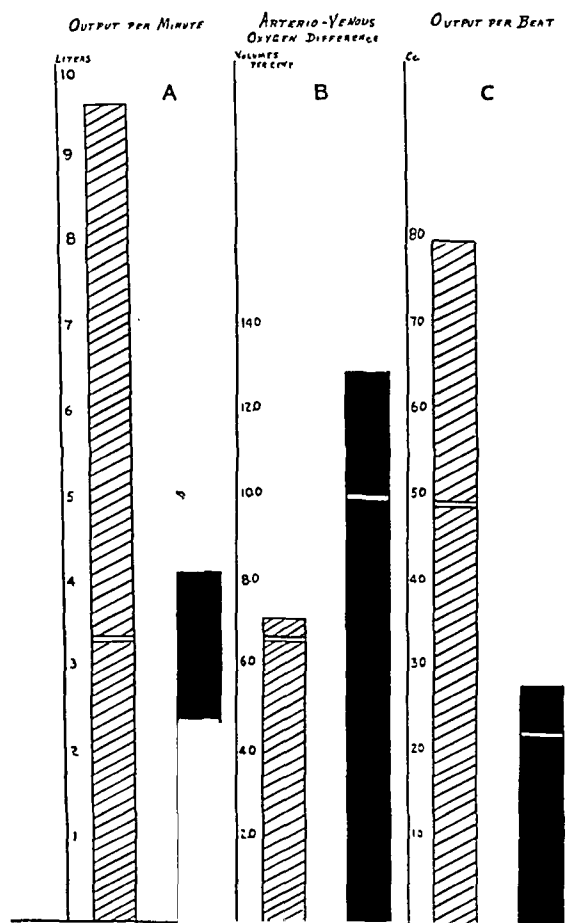


Fig. 4 (case 1).—Graphic comparison of the results of determinations of the cardiac output per minute (A), the arteriovenous oxygen difference (B) and the cardiac output per beat (C) of a normal control subject (shaded columns) and of the patient (solid columns) before and after exercise. The amount of change with exercise is shown by the height of the columns above the horizontal lines.

tissues was therefore lower, and the patient felt exhausted and short of breath. His pulse pressure remained at 12 mm. of mercury; that of the normal control rose from a resting value of 28 mm. to 40 mm. It was felt that this experiment substantiated our diagnosis of *concretio cordis*, because it offered evidence of the inability of the heart to dilate to a normal extent.

Treatment.—When we speculated as to the effect of digitalis in this case it was thought likely that it would have no beneficial effect. If the rate of 106 when the heart was at rest represented, as seemed probable, an increase compensating for the small volume per stroke, slowing of the heart by digitalis would diminish the cardiac output per minute still further and thereby increase the severity of the symptoms. Digitalis decreases the output of the heart per minute in normal dogs⁵ and in normal men.⁶ If the same effect resulted in this patient who already had an abnormally low output of the heart per minute, the influence would be for the worse. He gave a history of having been relieved by digitalis combined with rest during an earlier period of his illness. Accordingly digitalis was given, but with caution. After 1.6 Gm. of the leaf had been administered in three days, the patient complained of increasing dyspnea and distress. Two determinations of the cardiac output were made. The output of the heart per minute was reduced only slightly, and the decrease was mainly accounted for by a fall in the basal metabolic rate. The basal cardiac rate was 90, or 16 beats less than the previous average. This association of digitalization and slowing of the heart with increase in dyspnea and edema serves still further to emphasize the difference between this patient's condition and true heart failure.

The nature of the defect being thus established, the questions of prognosis and further treatment arose. Granting the accuracy of the diagnosis, it was clear that the patient's disability was severe, that it could be expected to grow worse rather than better, and that treatment by any method except mechanical relief would be in vain. If, however, enough of the confining coat of fibrous tissue could be removed to permit the heart increased freedom in relaxation, improvement might be expected. The attempt was made. The procedure is described by the operator in a second paper.

The patient died suddenly about twelve hours after operation.

Postmortem Observations.—The chief observations made at postmortem examination follow:

When the wall of the chest was opened, the heart was found to be small, and it was comparatively free from adhesions to the mediastinum, diaphragm and wall of the chest. The visceral pericardium and the parietal pericardium were closely fused throughout by fairly friable fibrous adhesions, but these could be separated by the finger. When the pericardium was opened, the parietal layer was found to measure from 2 to 3 mm. and the visceral layer from 1.5 to 2 mm. in thickness. Together they formed an inextensible fibrous capsule around the heart, as may be seen in figures 5 and 6. On cut section, the heart showed extreme atrophy, with brown, very friable muscular fibers. The endocardium was smooth and velvety, and there was no evidence of valvular disease. There was definite chronic passive congestion of the liver, spleen and kidneys, but not of the lungs.

5. Harrison, T. R., and Leonard, B. W.: The Effect of Digitalis on the Cardiac Output of Dogs and Its Bearing on the Action of the Drug in Heart Disease, *J. Clin. Investigation* 3:1, 1926.

6. Burwell, C. S.; Neighbors, DeWitt, and Regen, E. M.: The Effect of Digitalis upon the Output of the Heart of Normal Men, *J. Clin. Investigation* 5:125, 1927.

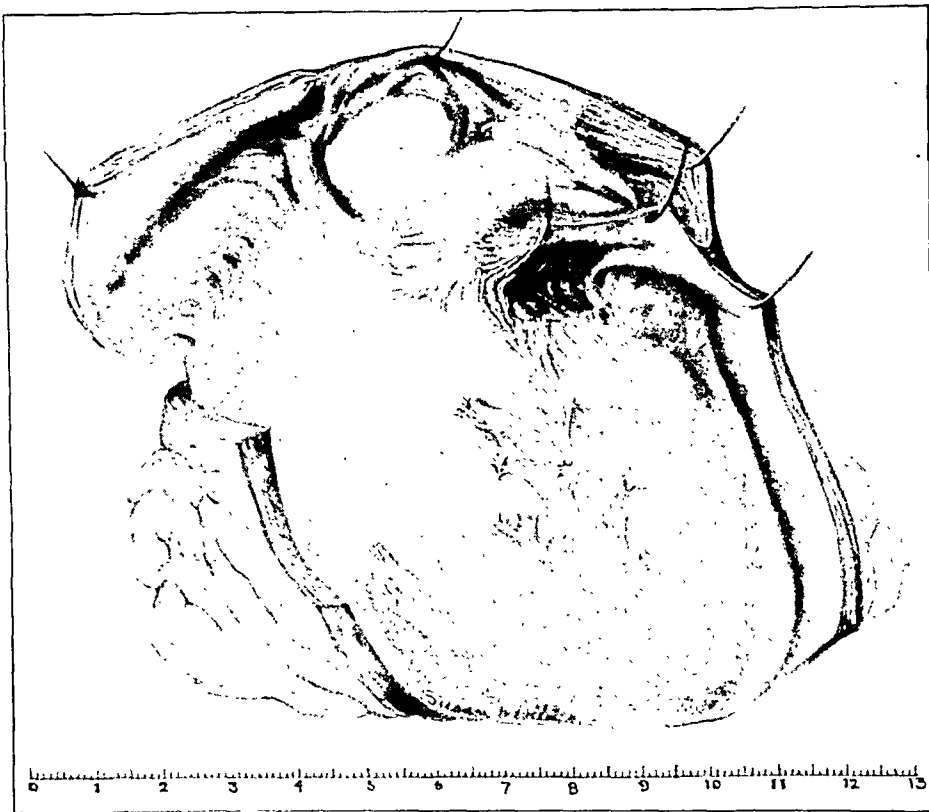


Fig. 5 (case 1).—Drawing of exterior surface of the heart of the patient, showing obliteration of the surface landmarks by the thickened epicardium, and the cut edge of the enormously thickened pericardium. The thinness of the muscular wall is shown by the tear in the region of the right ventricle.

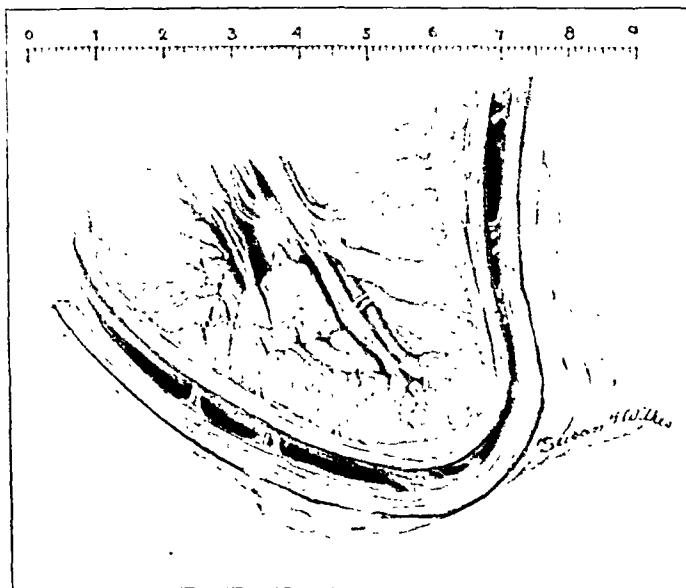


Fig. 6 (case 1).—Drawing of the cut surface of the heart of the patient, showing the small size, the atrophy of the cardiac muscle and the markedly thickened epicardium and pericardium.

In the microscopic examination of sections of the heart the thickened sections of both parietal and visceral pericardium showed evidence of chronic progressive proliferative tuberculous infection. Giant cells, small areas of caseation and an infiltration by mononuclears and lymphocytes were scattered diffusely throughout the sections.

This case, then, was one of tuberculous pericarditis resulting in the encompassment of the heart by a thick and closely applied layer of firm fibrous tissue. Experimental observations demonstrated certain deviations from normal in the functioning of the patient's heart. These deviations served to establish the diagnosis and also to supply a rational explanation of the symptoms and signs.

TABLE 4.—*Determinations of the Cardiac Output of the Patient in Case 1 Under "Basal" Conditions Before and After Digitalization*

Date and Conditions of Experiment	Surface Area, Sq. M.	Basal Metabolic Rate, per Cent	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference, per Cent by Volume	Cardiac Output				Pulse Rate per Minute	Respirations per Min.	Blood Pressure, Mm. Hg	Pulse Pressure, Mm. Hg
					Per Minute, Liters	Per Sq. M. of Surface Area, Liters	Per 100 Cc. of Oxygen Consumed, Liters	Per Beat, Cc.				
Average of 4 determinations under basal conditions before digitalization.....	1.71	— 2	240	10.04	2.41	1.41	1.00	22.8	106	20	96/83	13
Feb. 11, 1930, determination under basal conditions after 1.5 Gm. digitalis folia in 3 days	1.71	—10	212	9.10	2.33	1.36	1.10	25.0	93	17	94/84	10
Feb. 12, 1930, determination under basal conditions after 1.6 Gm. digitalis folia	1.71	—18	197	10.8	1.83	1.09	0.93	20.3	90	17	98/88	10

The essential defect, as revealed by these studies, was the limitation of the diastolic relaxation of the heart by the encircling scar tissue and the consequent fixation of the output per beat at an abnormally low level. This limitation of the output per beat made it impossible for the output of the heart per minute to increase except so far as this could be brought about by increase in the already rapid cardiac rate. The dyspnea that the patient experienced on slight exertion was presumably due to the inability of the heart to increase its output adequately, and thus resembled the dyspnea suffered by normal persons after severe exertion. The edema, however, was not due to the diminished cardiac output, but, certainly in the main, to the elevated venous pressure. That this is so is indicated by the distribution of the edema in the patient's body. The volume of blood flow per unit of time was necessarily diminished in both the peripheral and the pulmonary areas, but congestion

and edema were observed only in the area drained by the systemic veins in which the pressure is known to have been elevated far above the limits of normal. This is important enough to be restated: In the presence of diminished flow of blood through the lungs there were no physical signs of pulmonary edema during life nor any visible passive congestion in the lungs after death; massive edema occurred in the parts of the body in which the pressure in the veins was increased. This observation is of theoretical importance, since it tends to show that edema, a chief manifestation of heart failure, is more dependent on increased venous pressure ("back-pressure") than on alteration in the volume flow of blood.

Eyster⁷ emphasized the parallelism existing between the height of the venous pressure and the severity of the manifestations of cardiac failure. The fact that many symptoms and signs are common to this type of adhesive pericarditis (concretio cordis), on the one hand, and to congestive heart failure, on the other, may be explained by the existence of an abnormally high venous pressure in both groups of cases. The differences between the clinical manifestations of concretio cordis and those of congestive failure indicate that the increase of venous pressure may be brought about by different mechanisms.

Another patient with concretio cordis was the subject of similar studies, carried out some months after a successful decortication of the heart.

CASE 2.—History.—A 25 year old Negro entered Vanderbilt University Hospital on May 28, 1929, with a chief complaint of swelling of the abdomen.

The past history revealed good general health previous to the present illness. The patient had had measles, mumps, whooping cough and smallpox in childhood and pneumonia in 1922. He had received a stab wound in the right side of the chest near the upper border of the sternum five months previous to admission to the hospital. This had healed without any complications.

Except for the consumption of about 1 pint (about 250 cc.) of whisky a week during the past two years, the patient's personal habits had been good.

Three brothers were born dead, and a sister died soon after birth. The family history was otherwise unimportant.

The present illness began five months before admission to the hospital, when the patient noticed moderate swelling of his face on awakening in the morning. This would disappear in a few hours and after three weeks ceased to occur. During the latter part of December, 1928, swelling of the abdomen and legs was noted. This progressed rapidly and soon forced him to stop work. After two months he went to a hospital where he stayed six weeks and improved, the swelling of the abdomen and legs disappearing. Three weeks following his discharge this swelling reappeared and became persistent. There was moderate dyspnea on exertion, but no orthopnea and no cough. There had been slight transient precordial pains during the course of his illness.

Examination.—The patient was an intelligent Negro. He appeared moderately short of breath on exertion, showed evidence of marked weakness, and had slight

7. Eyster, J. A. E.: *The Clinical Aspects of Venous Pressure*, New York, The Macmillan Company, 1929.

fever with a daily swing from 98 to 100 F. There was a slight general glandular enlargement.

Examination of the head did not disclose any abnormality. The neck showed striking venous pulsations with bilateral distention of the veins.

There was evidence of hydrothorax on the right side. No cardiac impulses were palpable. The area of cardiac dullness was not enlarged. The sounds were distant, and no murmurs or friction rub could be heard. There was no demonstrable shift in the position of the heart with change in the position of the body. The rhythm was regular, the rate 100 and the blood pressure 110 systolic and 80 diastolic.

The abdomen was distended with fluid, and the liver was markedly enlarged. There was pitting edema of the extremities.

TABLE 5.—*Determinations of Cardiac Output of the Patient in Case 2 Under Basal Conditions and Following Exercise Twelve Months Following Operation for Concretio Cordis*

Date and Conditions of Experiment	Surface Area, Sq. M.	Basal Metabolic Rate, per Cent	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference, per Cent by Volume	Cardiac Output				Pulse Rate per Minute	Respirations per Min.	Blood Pressure, Mm. Hg	Pulse Pressure, Mm. Hg
					Per Minute, Liters	Per Sq. M. of Surface Area, Liters	Per 100 Cc. of Oxygen Consumed, Liters	Per Beat, Cc.				
May 21, 1930, under basal conditions	1.61	+ 1	219	6.29	3.48	2.16	1.59	43	80	22	90/55	35
May 23, 1930, under basal conditions	1.61	+ 1	220	6.11	3.6	2.24	1.64	46	79	18	85/48	37
June 4, 1930, after exercise	1.61	+212	670	8.77	7.64	4.73	1.31	68	112	40	110/78	32
June 6, 1930, after exercise	1.61	+212	678	8.37	8.10	5.02	1.19	81	100	34	112/78	34

The results of examination were otherwise negative.

The urine was normal, except for a trace of albumin on one occasion. The cells of the blood were normal. The Wassermann reaction was negative.

A phenolsulphonphthalein renal test with intravenous administration of dye showed an excretion of 80 per cent of the dye in two hours.

An x-ray picture of the chest showed increased density over the right lower lobe, suggesting a small amount of fluid. No evidence of calcification of the pericardium could be made out.

An electrocardiogram showed a rate of 100, a P-R interval of 0.16 second and inverted T waves in all leads. Tracings made with the patient in different positions showed very slight shift of the electrical axis.

In view of the findings, a diagnosis of concretio cordis was made, and because of the patient's complete disability an operation was advised.

The operation and the patient's subsequent course are discussed in a second paper. It was during his third admission to the hospital, in June, 1930, that studies on the cardiac output were made.

Observations of venous pressure and cardiac output were not made in this case before operation, but similarity in the manifestations of

the two cases make it certain that the venous pressure was high and probable that the cardiac output per minute and per beat was diminished. Twelve months after operation these studies were carried out, at a time when the patient had no edema, no dyspnea and no enlargement of the liver. As may be seen in table 5, the results show no essential deviation from the average normal values. The venous pressure was within normal limits.

Therefore, it can be said that in one patient with concretio cordis and congestion the venous pressure was high and the cardiac output per minute and per beat was low, while in another patient successfully operated on for a similar condition there was no congestion and the venous pressure and the output per beat were within the limits found in normal subjects.

Since the writing of this paper there has appeared a report of the impressive work of Beck and Griswold.⁸ These observers were able to produce experimentally in dogs "fibrosis and contracture of the parietal pericardium, or epicardium, or both, forming a casing of scar which compresses the heart and primarily obstructs its filling" The development and contracture of the scar tissue were accompanied by a rise in venous pressure and by ascites, hydrothorax and edema, pulmonary and subcutaneous; the pulse became small and rapid, and the output of the heart per minute was decreased. Resection of the scar was followed, in general, by a fall in the venous pressure toward the normal level, by a diminution or disappearance of edema and by an increase in the output of the heart per minute. After operation, in most cases the heart was larger than before. These authors also reported a case similar in type to the two reported here. Their patient exhibited, before operation, a high venous pressure, a rapid pulse and a small pulse pressure. After pericardiectomy the venous pressure and the pulse rate fell, and the pulse pressure rose to twice its former value.

The observations of Beck and Griswold on dogs seem both to confirm and to be confirmed by our studies on patients, particularly in regard to the high venous pressure and the diminished output of the heart.

SUMMARY

In a patient with concretio cordis studies of the output of the heart and of the venous and arterial pressures seemed to indicate that the essential defect in the circulatory mechanism was the failure of the heart to relax (dilate) to the normal extent. Similar studies of a patient successfully treated by operation for a similar condition revealed no departure from normal.

8. Beck, C. S., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome, *Arch. Surg.* **21**:1064 (Dec., pt. 2) 1930.

PLASTIC OPERATION FOR ANAL INCONTINENCE

FURTHER REPORT*

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BALTIMORE

Within the last three years, Wreden¹ and I² described a new method of restitution of anal control following damage or loss of the sphincter muscle. At that time Wreden reported one successful case, and I reported one successful and one unsuccessful case; since then Ransohoff³ has reported an additional case in which this method was successful. My purpose in the present paper is to record five other cases, to call attention again to this valuable principle of treatment in a most discouraging situation and to introduce some further modifications of technic which seem to be improvements. The essential principle of Wreden's operation is to harness the two gluteus maximus muscles by slings of fascia that pass around the anal canal, in such a manner that when the glutei contract these fascial slings will be drawn taut. As the slings from the two sides interlock, this tightening closes the anal canal and gives the patient voluntary control over the closure of the lower end of the bowel.

REPORT OF CASES

The case reports, condensed to essentials, follow.

CASE 1.—Mrs. E. M., white, aged 44, was admitted to the Church Home and Infirmary, with the complaint of diarrhea and incontinence of feces. She had a long surgical history of twelve operations, including removal of a ruptured appendix, removal of the gallbladder, cesarean section, hysterectomy, perineal repair and several rectal operations. Three years previous to her admission for the present illness, the sphincter muscle had been divided for an ulceration of the rectum. Since that time she had had no control over the bowels in spite of two or three attempts at repair of the sphincter. Eighteen months before admission diarrhea developed with from twenty to forty stools daily. Parasites were not found on repeated search, and ulceration was not seen. A diagnosis of mucous colitis was made.

On examination, the patient was found to be a highly nervous woman with multiple scars and an extremely annoying mucous colitis. The anal outlet was patulous and showed considerable scarring. On palpation, no sphincteral tone

* Submitted for publication, Dec. 26, 1930.

1. Wreden, R. R.: A Method of Reconstructing a Voluntary Sphincter Ani, *Arch. Surg.* **18**:841 (March) 1929.

2. Stone, H. B.: Plastic Operation for Anal Incontinence, *Arch. Surg.* **18**:845 (March) 1929.

3. Ransohoff, J. Louis: *Ann. Surg.* **90**:317, 1929.

could be felt, and when the patient was asked to contract the anal outlet voluntarily, visible contraction did not take place.

On Oct. 18, 1929, an operation was done with the technic described in my previous article, except that a piece of fascia from the patient's thigh was used to form the strips. The wound became infected to a considerable extent, and some of the fascia sloughed out. It finally healed, and the patient was discharged six weeks after operation. At this time the mucous colitis was greatly improved, and there was distinct contracting power in the anal canal when the gluteus muscles were tightened. A report one year later showed much improvement over her previous condition, and her control was considered about 85 per cent. This case can be classed as one of definite improvement.

CASE 2.—L. deG., a girl, white, aged 16, was admitted to the Church Home and Infirmary. She had a spina bifida with paralysis of many of the muscles in both legs below the knee with pes equinovarus and with incontinence of the rectum and of the bladder; this condition had existed since birth and was clearly due to a developmental fault in the lower part of the spine, with extensive disturbance of the nerves.

On Jan. 14, 1930, operation was performed, the strips being of prepared fascia and not autogenous. The wound healed practically per primam except for a slight serous drainage. The patient was discharged on January 28, and at that time the result of the operation was considered to be very good. She has been seen since that time, and as she had learned to utilize the gluteus muscles better, her improvement has continued. The patient considers the result to be practically perfect.

CASE 3.—H. H., white, a man, aged 63, was admitted to the Church Home and Infirmary. In September, 1928, he was operated on for an extensive anal fistula. In the course of this operation it was necessary to divide the sphincter muscle. The fistula healed, but following recovery from the operation there was considerable incontinence but not complete loss of anal control. This weakness of control was quite annoying, particularly as this patient also had a mucous colitis of several years' standing and was unable to retain mucous stools at times.

Operation was done on March 25, 1930, the prepared fascia being used for the strips. He was discharged on April 7. The wound healed practically per primam, there being only a slight amount of serous drainage. The man's condition was greatly improved. When he was seen again three months later, the result was satisfactory but not perfect. The only difficulty that the patient has is that there is some slight seepage of moisture unless he is careful to keep his glutei tense at times. This occurs only when one of the mucous bowel movements is present in the rectum. He does not have any difficulty controlling actual stool nor any difficulty with gas.

CASE 4.—Mrs. J. O., white, a woman, aged 37, was admitted to the Union Memorial Hospital on March 16, 1930, with a diagnosis of ovarian cyst, uterine myomas and also of relaxed sphincter ani. Operation was done on April 22, the uterus and the right adnexa being removed. Convalescence from this operation was satisfactory, and on April 19 it was decided to attempt a plastic operation for the anal incontinence with strips of fascia. This incontinence followed forceps delivery in 1912; in 1913 an unsuccessful attempt was made to repair the damage by the usual plastic operation on the perineum. A second unsuccessful attempt at sphincter repair was made in 1921. The incontinence had continued without improvement and had recently become worse. The operation on April 19, 1930, was performed by Dr. J. Arthur Weinberg, at that time resident surgeon of the

Union Memorial Hospital. Following the operation, the wounds became slightly infected and drained for two or three weeks before finally closing. There was also some sloughing of the distal end of the rectal mucosa, which was probably due to some strangulation by the bands of fascia. The patient was discharged from the hospital on May 11 with the wound entirely healed; she had good control of the bowel movements but not complete control of gas. The sphincter at that time admitted the index finger. She was reexamined on Oct. 24, 1930, when the following note was made: "Sphincter tone good. Admits index finger. Wounds entirely healed. Patient has complete control except when she becomes very nervous and excited. Bowels move regularly. No soiling whatever. Result considered perfect."

CASE 5.—C. B., white, aged 32, was operated on in 1928 and again in 1929 for a rectal fistula. Since that time he had been troubled with discharge and itching about the anus and was unable to control his bowel movements after taking laxatives. He was first given an injection of alcohol for the pruritus, but he returned later complaining of incomplete control of the bowel. On rectal examination, an inflamed area was seen about the anus with a mucoid discharge coming from the rectum. The rectal sphincter was relaxed, and the patient apparently had very little control of it. Operation was performed on March 4, 1930, at the Church Home and Infirmary by Dr. Ervin B. Wallace, at that time resident surgeon at the Church Home. The material used for the strips was prepared fascia. Recovery was uneventful, and the wounds healed by first intention. The discharge from the rectum was considerably lessened. Sphincter control improved so much that the patient could now hold an enema. He was discharged from the hospital in two weeks and seen again in the middle of October, 1930, six months after the operation. He still had some pruritus in the skin about the anus, but his sphincter was working perfectly. Dr. Wallace reports an entirely satisfactory result. In this instance the patient was distinctly subnormal mentally, and it was felt that because of his lack of intelligence he did not utilize his gluteus muscles to the best possible advantage.

Summary.—In the five cases reported, together with the four others reported in the articles previously referred to, the results were as follows: successful, five cases; practically successful, two cases; decidedly benefited, one case, and failure, one case. In the two in which the results were the least satisfactory, infection was much more pronounced than in any of the other cases, and it was felt to be without doubt the cause of failure. The desire to reduce the possibility of infection in a field where strict aseptic postoperative conditions are almost impossible has led to the modification of the operation in some details, and at present the following procedure is employed.

OPERATIVE PROCEDURE

With the patient in lithotomy position, after as careful cleansing of the field as possible, including cleansing enemas for two days previous to operation, two symmetrical incisions are made, one on each side, about 4 cm. lateral to the anal margin and slightly posterior to it. These incisions slant somewhat laterally toward their anterior ends, are about 2 cm. long and are carried well into the subcutaneous fat. After the two incisions have been made, a closed long curved

clamp (Kelly) is introduced through one incision and by blunt dissection is forced around through the subcutaneous tissues in front of the anus, and its tip is made to emerge into the other incision. The clamp is then opened and grasps the ends of two strips of fascia, 0.5 cm. wide and from 22 to 25 cm. long. This fascia may be either autogenous from the patient's fascia lata or prepared by the Koontz method. The clamp grasping the strips of fascia is then withdrawn the way it

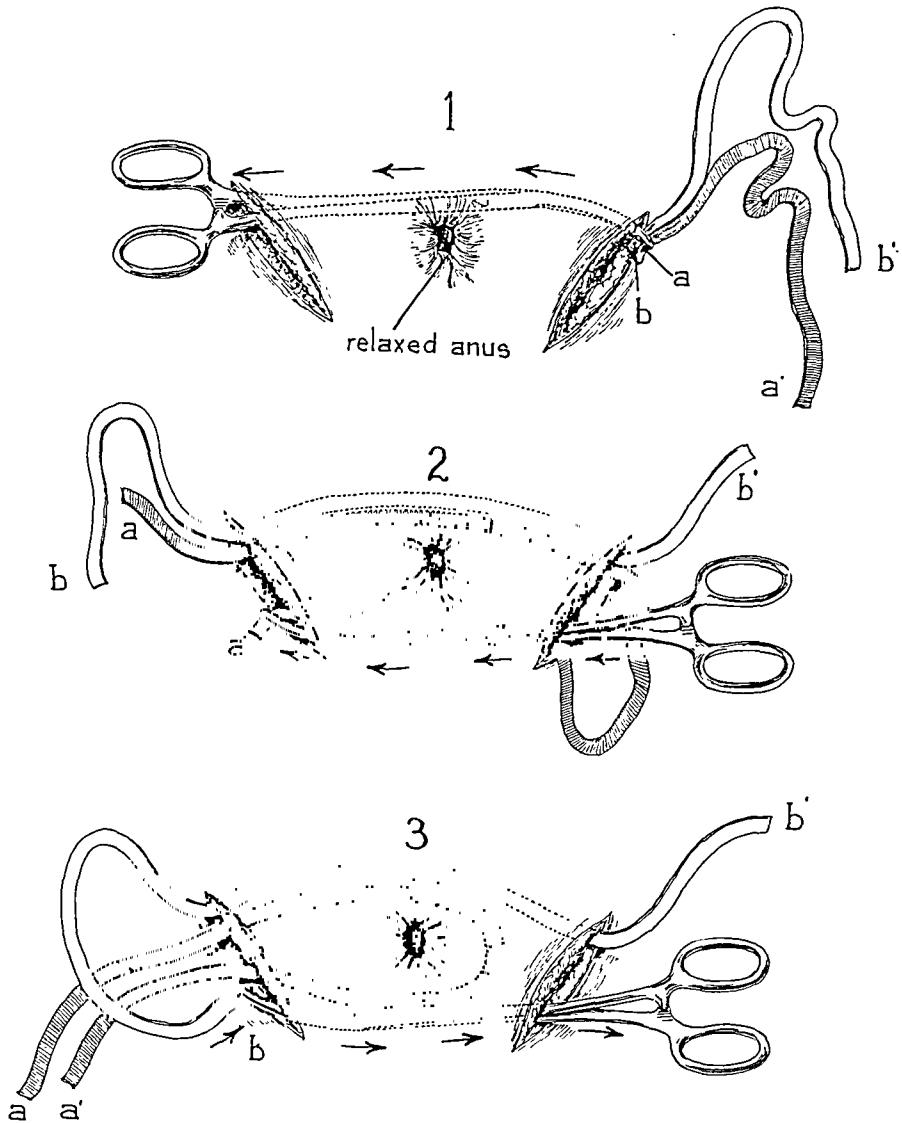


Fig. 1.—Steps in the plastic operation for anal incontinence: 1, clamps are passed subcutaneously in front of the anus grasping the strips of fascia and are about to be pulled from one side to the other; 2, both strips are passed subcutaneously in front of the anus and one posteriorly; 3, the loops of fascia encircle the anus subcutaneously in opposite directions.

was introduced. This threads both strips of fascia in front of the anus. A second Kelly clamp now grasps the end of one of the strips, is passed again into one of the incisions and is forced to burrow its way subcutaneously to the other incision, this time behind the anal canal. As it emerges into the opposite wound,

the strip of fascia clamped in its tip is seized and more of it drawn through the wound. This strip now encircles the anus subcutaneously, entering at one incision, and its opposite end emerging from the same incision. The clamp, which meanwhile has remained in its posterior tunnel, is opened, grasps the free end of the second strip of fascia and is pulled back the way it was pushed in. It brings back with it the end of the second strip of fascia which now also encircles the anus subcutaneously, but in the opposite direction to the first strip, each forming

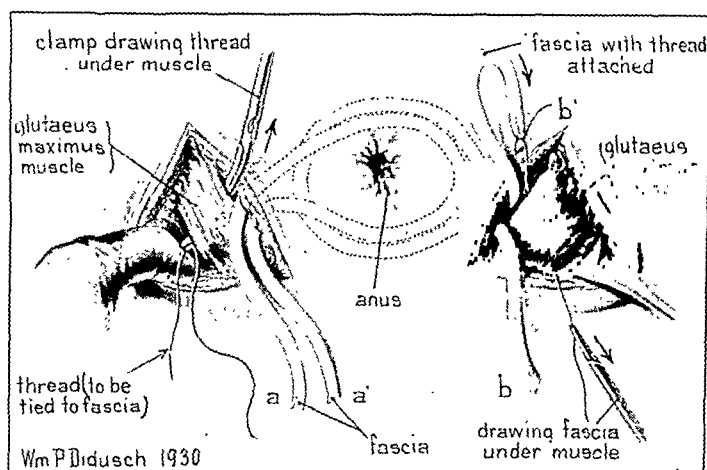


Fig. 2.—The outer ends of the strips of fascia are passed around the bundles of the gluteus muscle.

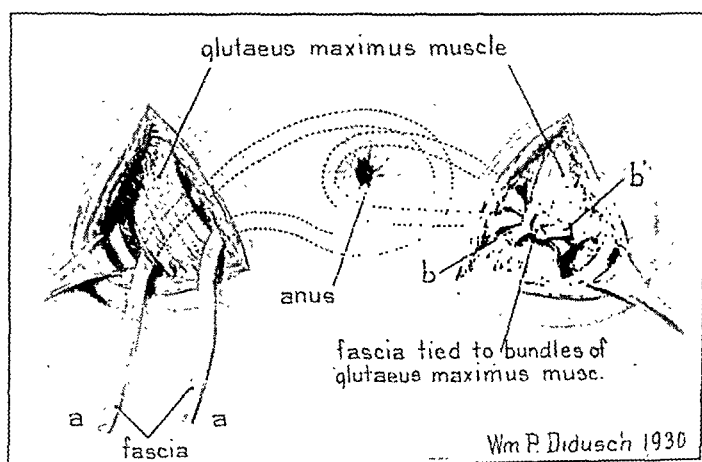


Fig. 3.—The loops of fascia are tied on the right side, ready for tying on the left.

a loop with the free ends of the same strip protruding through the same incision. From one of the incisions, blunt dissection is now carried outward and backward fairly deep in the fat until the mesial edge of the gluteus maximus is reached and identified. A bundle of fibers of this muscle about as thick as one's index finger is now surrounded by one end of the strip of fascia protruding from the incision. This may be done easiest by carrying a linen thread in an aneurysm needle around the muscle bundle and using the thread as a tractor, tied to the end of the strip of fascia, to pull the strip around the muscle bundle. This end of the strip is

now brought back into the incision and tied tightly to its own other end, thus forming a closed loop, one end of which encircles the anal canal and the other encircles a bundle of gluteus muscle. Exactly the same steps are executed in the other incision with the two ends of the other strip of fascia. The knotted ends of the fascia sink into the depths of the wounds, and the skin is closed as the operator may prefer. The two small incisions are sealed with some impervious dressing, and the bowels are kept tied up for from seven to ten days following the operation.

The anus is now encircled by two loops of fascia, running off into opposite directions, tied under some tension about bundles of gluteus muscles. When the glutei are voluntarily contracted they will pull the loops still tighter and give a mechanism for voluntary increase in closing pressure on the anal canal.

As has been said, the principle of this operation is that of Wreden. The method differs from his and from my own first method by reducing the number of incisions from four to two and by moving these two further from the anal orifice. The mechanics of the operation remain the same, but the chance of avoiding infection of the wound is improved. The results in the last four cases herewith reported, in which this newer modification was used, have been very satisfactory. If infection can be avoided, the percentage of good results should be high.

There are several points of interest in regard to this operation that deserve a further word. The operation depends on the utilization of the glutei muscles. It is obvious that if these muscles for any reason are not functioning, this operation cannot be expected to succeed. Also, until the patient learns to use the glutei properly, the full benefit is not obtained. Hence education of the patient in this regard is important. He must be trained to contract the buttocks when necessary. It follows that patients who cannot be taught to do this, because of lack of interest or intelligence, do not improve as much as others. The last case reported was an instance in point. The anatomic and surgical result was excellent, but the patient did not always remember to use his new power of anal control. Because of this necessity for education, the patients in successful cases do not show as much improvement immediately as they will ultimately.

SUMMARY

Five further cases of anal plastic operations are reported and reviewed with four previously recorded cases; the results in five were excellent, in two good and in two unsatisfactory. A further modification of the method to secure better protection against infection is described.

PEPTIC ULCER IN EXPERIMENTAL OBSTRUCTIVE JAUNDICE *

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During the course of our studies on the experimental control of ascites, extending over several years, we have had occasion to observe a large number of dogs with complete obstructive jaundice. Many of these animals were lost to the original study because of the early development of perforated duodenal and gastric ulcers. Only a few studies have been made concerning ulcer complicating complete obstructive jaundice. Of the recent work bearing directly on the subject, Berg and Jobling¹ (1930) found that in three of five animals, peptic ulcers developed following complete obstructive jaundice. In one dog multiple gastric erosions were encountered forty-seven days after ligation of the common bile duct. One hundred and eight days after operation, another animal had two perforated chronic duodenal ulcers, and the third dog had a single chronic duodenal ulcer after one hundred and eighty-nine days. These authors also often found peptic ulcers in animals with biliary fistulas, and have referred to the recent literature on the formation of ulcer following exclusion of bile from the intestine.

METHOD OF EXPERIMENTATION

Under ether anesthesia and with aseptic technic, obstructive jaundice was produced by double ligation and section of the common bile duct. The gallbladder was also removed from most of the animals, and from one to three lobes of the liver were removed at the same time from a small number. The animals were then maintained on a diet of dog biscuits, milk and corn syrup, with an occasional feeding of meat in a few instances; a few animals were given a coarser diet consisting of a cooked mixture of ground corn meal, ground bone and meat scraps. The latter diet was instituted to determine the effect of the rough element in the food on the production of ulcer.

Frequent examinations were made of the feces of these animals, and the absence of bile from the gastro-intestinal tract was verified by tests for urobilin. Only occasionally an animal showed evidence of reestablishment of biliary drainage into the intestine, and in such animals it was clearly manifest by the normal color of the stools, urobilin in the feces and the complete disappearance of the serum bilirubinemia.

* Submitted for publication, March 9, 1931.

* From the Division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers: An Experimental Study, Arch. Surg. **20**:997 (June) 1930.

RESULTS OF EXPERIMENTS

Necropsy of sixty-four animals from five to two hundred and ninety-five days following ligation of the common bile duct showed acute, subacute or chronic peptic ulcer of the duodenum or stomach. During the same period only twenty-three animals died of causes attributable to this operation without showing gross evidence of peptic ulcer; their deaths occurred from twenty-one to one hundred and ninety-five days following ligation of the common bile duct. These data are summarized in tables 1 and 2.

The gross appearance of the ulcers were varied; some appeared as acute perforations with little, if any, reaction at the margins of the perforation. The other extreme was characterized by the typical crater ulcer with overhanging edges and indurated base. In general, the ulcers that seemed most acute occurred in the early months of jaundice, but in some cases moderately indurated ulcers of the subacute type were found after from three to six weeks of obstructive jaundice. Again, acute perforating ulcers have been noted after eight months of jaundice, and in some cases acute perforations were found associated with another ulcer that appeared quite chronic, and in one specimen, an acute erosion had passed through a portion of a definite subacute gastric ulcer.

Of the sixty-four animals with peptic ulcer, eight had gastric ulcers, which, with one exception, were on the pylorus and were almost all bordering on the line of the lesser curvature of the stomach. One perforating ulcer was situated at the incisura on the line of the lesser curvature. In five cases both gastric and duodenal ulcers were present. Sixty-one animals had duodenal ulcers, thirty-eight of which appeared to be single; twenty-three animals had from two to four ulcers. The duodenal ulcers were situated about 1 cm. beyond the pylorus, slightly anterior to the line of the lesser curvature of the stomach. Some ulcers showed a definite tendency to encircle the duodenum a short distance beyond the pylorus. If a second duodenal ulcer was present, it was about 1 cm. below the first ulcer and approximately on the opposite side of the duodenum. A third ulcer, if present, was below the second and again on the opposite side of the duodenum.

That these ulcers are not the result of trauma at the time of operation is evidenced by the fact that many of the animals did not show evidence of ulcer for many months after operation. Also, in a large number of animals denervation of the liver was accomplished by stripping the adventitia from the hepatic artery, portal vein and common bile duct, with section of all the other structures of the gastrohepatic omentum. Many of these animals have survived for more than two years, and peptic ulcers have not been observed in any case.

TABLE 1.—*Peptic Ulcer in Dogs Following Ligation of the Common Bile Duct*

Dog	Weight, Kg.	After Ligation, Days	Ulcers Present	Probable Cause of Death
1	11.5	5	1 duodenal.....	Peritonitis
2	7.8	6	2 duodenal.....	Distemper
3	9.4	8	1 duodenal.....	Perforation
4	6.0	8	3 duodenal.....	Perforation
5	20.0	9	4 large duodenal.....	Perforation
6	6.8	10	1 duodenal.....	Perforation
7	7.3	13	1 duodenal.....	Perforation
8	15.1	14	2 duodenal.....	Perforation
9	10.2	15	2 duodenal.....	25 per cent of liver also removed; peritonitis
10	8.8	15	2 duodenal.....	25 per cent of liver also removed; perforation
11	13.4	17	2 duodenal.....	Perforation
12	5.9	21	1 duodenal.....	Perforation
13	6.4	23	1 duodenal.....	Intestinal hemorrhage
14	7.4	24	2 duodenal.....	Rupture of biliary duct
15	7.2	25	2 duodenal.....	Perforation
16	13.0	27	2 duodenal.....	Anemia
17	7.6	28	3 duodenal.....	Perforation
18	9.2	28	1 duodenal.....	Rupture of biliary duct
19	8.5	29	1 duodenal; 1 pyloric....	Intestinal hemorrhage
20	6.0	30	1 duodenal.....	Perforation
21	10.1	31	1 healing duodenal.....	Intestinal hemorrhage
22	9.2	35	1 duodenal.....	30 per cent of liver also removed; perforation
23	5.2	35	1 duodenal.....	Intestinal hemorrhage
24	14.5	36	1 duodenal.....	Intestinal hemorrhage
25	14.4	39	1 duodenal.....	Inanition
26	15.1	39	1 duodenal.....	Perforation
27	12.6	41	2 duodenal.....	Perforation
28	6.0	41	1 pyloric.....	Hemorrhage from ulcer
29	6.8	42	1 healing duodenal.....	Intestinal hemorrhage
30	8.2	43	1 duodenal.....	Intestinal hemorrhage
31	19.8	47	2 duodenal.....	Perforation
32	7.5	55	1 duodenal.....	Perforation
33	10.9	59	1 duodenal.....	Subdiaphragmatic abscess
34	17.3	60	1 duodenal.....	Perforation
35	13.5	60	1 duodenal.....	Hemorrhage from ulcer
36	6.7	63	2 duodenal.....	30 per cent of liver also removed; perforation onto liver
37	18.2	66	1 duodenal.....	Empyema
38	6.2	68	1 healing duodenal.....	35 per cent of liver also removed; inanition
39	10.5	70	2 duodenal; 1 pyloric....	Intestinal hemorrhage
40	9.9	72	1 duodenal.....	Hemorrhage from ulcer
41	9.3	76	1 duodenal.....	Perforation
42	24.0	78	2 duodenal.....	50 per cent of liver also removed; anemia
43	7.6	81	2 duodenal.....	Perforation
44	7.2	81	1 duodenal.....	35 per cent of liver also removed; subdiaphragmatic abscess
45	6.5	84	2 duodenal.....	60 per cent of liver also removed; perforation
46	15.4	85	1 healing duodenal.....	Hemorrhage from ulcer
47	5.4	85	1 pyloric.....	Inanition
48	10.7	87	1 duodenal.....	Perforation
49	11.8	88	1 duodenal.....	Perforation of ulcer into gallbladder
50	4.7	93	1 duodenal.....	Perforation
51	9.9	98	1 duodenal.....	Hemorrhage in stomach
52	3.4	101	1 duodenal.....	Inanition
53	15.3	112	1 healing duodenal.....	Cholangitis
54	6.5	118	2 duodenal; 1 gastric....	Perforation
55	17.0	121	1 duodenal.....	35 per cent of liver also removed; intestinal hemorrhage
56	9.2	128	1 duodenal.....	35 per cent of liver also removed; intestinal hemorrhage
57	13.5	136	2 duodenal; 1 gastric....	Perforation
58	6.0	159	1 pyloric.....	25 per cent of liver also removed; inanition
59	6.7	168	2 duodenal.....	Hemorrhage from ulcer; 35 per cent of liver also removed
60	6.5	174	1 duodenal; 1 pyloric....	Inanition
61	13.5	176	1 duodenal.....	50 per cent of liver also removed; anemia
62	5.5	179	1 duodenal.....	30 per cent of liver also removed; anemia
63	20.6	235	1 duodenal.....	Infection of biliary tract
64	8.2	295	1 duodenal.....	35 per cent of liver also removed; intestinal hemorrhage

COMMENT

We have eliminated from consideration here a large number of animals in which the common bile duct had been ligated. In a very few animals, biliary connection was reestablished to the gastro-intestinal tract and relief from jaundice was afforded. Many others that had been jaundiced for several months died as the direct result of other experiments. Only a small percentage of these animals had peptic ulcer, but since their death was due to causes other than sequelae of the ligation of the common bile duct, this entire group was not considered. From the data presented it is evident that the occurrence of peptic ulcer depends on factors not directly related to the duration of jaundice. From

TABLE 2.—*Dogs Without Gross Peptic Ulcer Following Ligation of the Common Bile Duct*

Dog	Weight, Kg.	After Ligation, Days	Probable Cause of Death
1	10.2	22	Intestinal hemorrhage and anemia
2	9.2	22	Perforation of biliary duct
3	4.9	27	Gastric and duodenal hemorrhage
4	8.9	29	Gastric hemorrhage
5	9.4	31	Perforation of biliary duct
6	6.1	40	Inanition
7	6.0	40	25 per cent of liver also removed; intestinal hemorrhage
8	5.4	43	Inanition
9	7.1	49	Perforation of biliary duct
10	6.9	51	Intestinal hemorrhage
11	7.8	68	Intestinal hemorrhage
12	10.9	71	Cholangitis
13	11.3	80	Inanition
14	9.0	89	30 per cent of liver removed; inanition
15	15.5	93	Pulmonary edema; ascites
16	10.8	95	40 per cent of liver also removed; inanition
17	10.7	114	50 per cent of liver also removed; inanition
18	5.1	119	Intestinal hemorrhage
19	10.7	132	Inanition
20	6.4	133	Bronchopneumonia
21	7.8	141	25 per cent of liver also removed; inanition
22	5.0	142	Inanition
23	5.2	195	Intestinal hemorrhage

the data that we have not included we could add further evidence similar to that in our group of jaundiced animals that died without the development of ulcer. These animals demonstrate that with complete obstruction of biliary outflow, life may continue for several months without the formation of ulcer. Several of our jaundiced animals have died as the result of other experiments after eleven months of obstructive jaundice, and few in this particular group showed evidence of peptic ulcer.

The most common cause of death in these jaundiced dogs was perforation of a peptic ulcer with resultant peritonitis. The next most common cause of death was hemorrhage into the gastro-intestinal tract; for the most part this was evidenced by chronic oozing with fresh blood in the feces or tarry stools. In some instances there were several periods of intestinal bleeding, with remissions and subsequent improvement in

the general condition of the animal. Transfusion was resorted to in many instances, after which blood usually continued to appear in the stools for two or three days and then was absent for a few weeks. Intramuscular injection of from 5 to 10 cc. of whole blood also seemed to be effective in bringing about remission, but several animals continued to bleed until death. In some animals massive hemorrhage occurred from the site of the peptic ulcer.

Definitely diminished resistance to the formation of ulcer appears to be present following ligation of the common bile duct. This may be due at least in part to the exclusion of bile from the gastro-intestinal tract. Kapsinow² (1926) found that in seventeen of forty-three dogs, duodenal ulcer developed in about two weeks following anastomosis of the gallbladder to the renal pelvis and ligation of the common bile duct. We have not been successful in preventing the formation of ulcer in a number of dogs by oral administration of gallbladder bile twice daily. It should be noted, however, that such administration of bile differs greatly from the normal flow into the intestine, and that it was administered to dogs that already had complete biliary retention.

Dietary factors play a definite part in the formation of peptic ulcer in dogs with obstructive jaundice. For the most part, in our animals maintained on a bland diet of milk, syrup and bread, ulcer did not develop nearly as soon as in others maintained on a coarser diet of cooked corn meal, meat and ground bone. We are inclined to attribute this difference to the mechanical factors of the formation of ulcer, although chemical factors are probably also concerned. One striking observation should be mentioned in this respect: most of the animals that died of acute perforation of an ulcer were those that maintained an excellent appetite and always ate their food rapidly; thus ulcers were found in well nourished animals up to a few days before death. On the other hand, many of the animals lost appetite and weight, and died without the formation of ulcer. With the exceptions mentioned, all of our animals were given the same food, and all were kept under the same hygienic conditions for the entire period. However, there was a definite tendency for ulcers to form in groups of animals; that is, the lapse of several weeks without the death of an animal from ulcer would be followed by several deaths in the same week without reference to the duration of jaundice. We have been unable to ascribe this periodicity to diet, hygienic conditions or other known factors.

We do not feel justified in attempting to interpret our observations of jaundiced dogs in relation to the occurrence of peptic ulcer in man. It is obvious that diminished resistance to the formation of ulcer is pri-

2. Kapsinow, Robert: The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestine, *Ann. Surg.* **83**:614 (May) 1926.

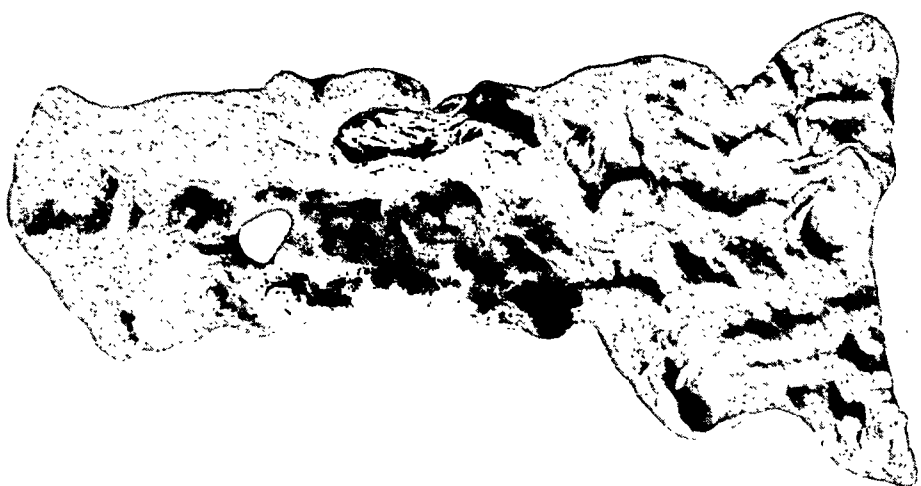


Fig. 1.—Pylorus and duodenum opened along the line of the greater curvature of the stomach, nine days after ligation of the common bile duct. The animal died of peritonitis subsequent to the perforation of the ulcer.

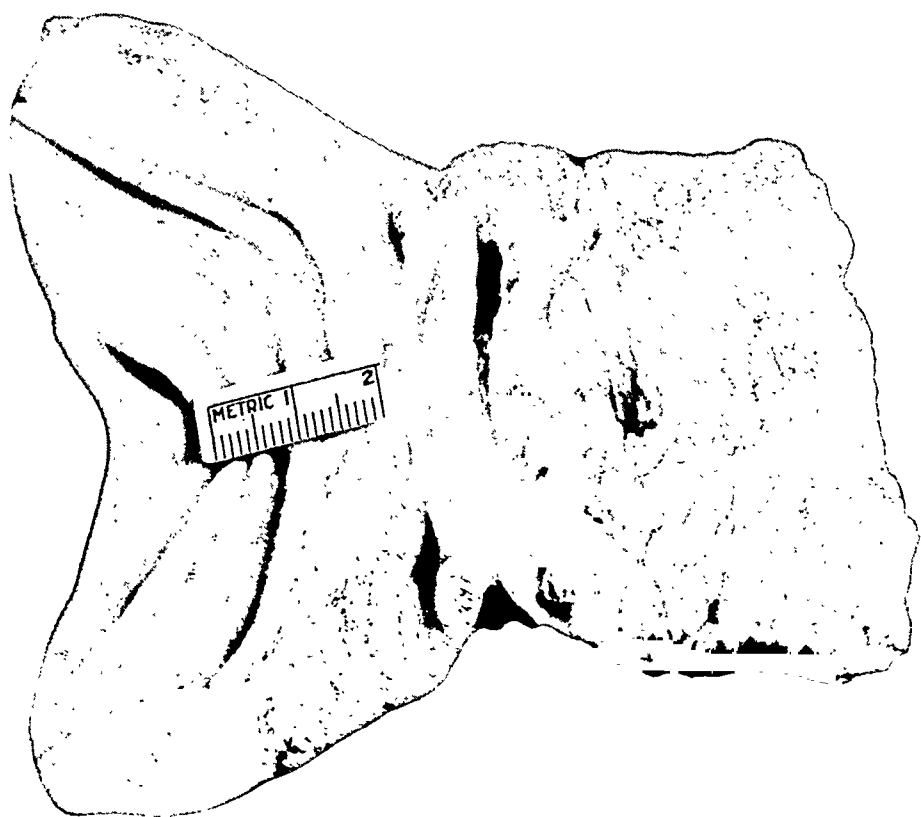


Fig. 2.—Pylorus and duodenum seventy-eight days after ligation of the common bile duct and removal of approximately 50 per cent of the liver. Severe anemia contributed to the cause of death in this animal.

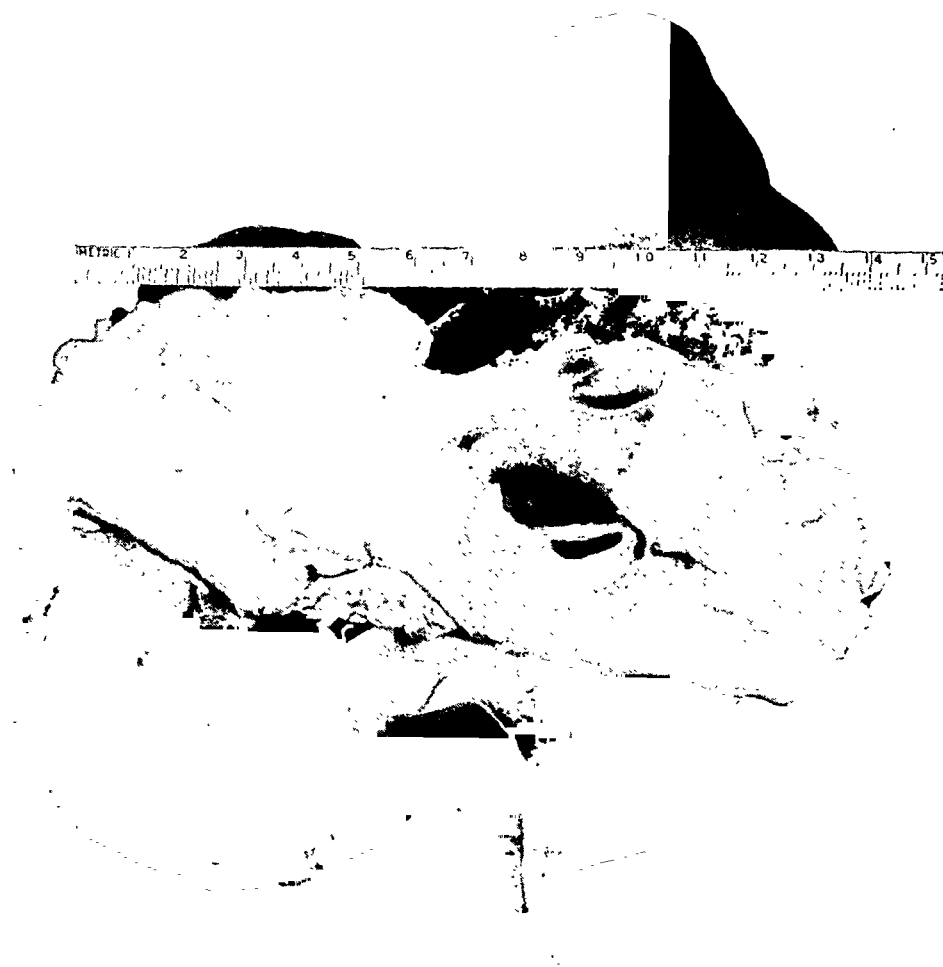


Fig. 3.—Pylorus and duodenum on the liver of a dog eighty-seven days after ligation of the common bile duct. Two duodenal ulcers were present, one of which has perforated into the gallbladder. The animal died of inanition.



Fig. 4.—Stomach and duodenum from a dog one hundred and eighteen days after ligation of the common bile duct. Acute perforation developed on the base of an apparently older gastric ulcer.



Fig. 5.—Stomach and duodenum one hundred and twenty-one days after ligation of the common bile duct and removal of approximately 35 per cent of the liver. The animal was killed at this time so that specimens of tissues could be obtained.

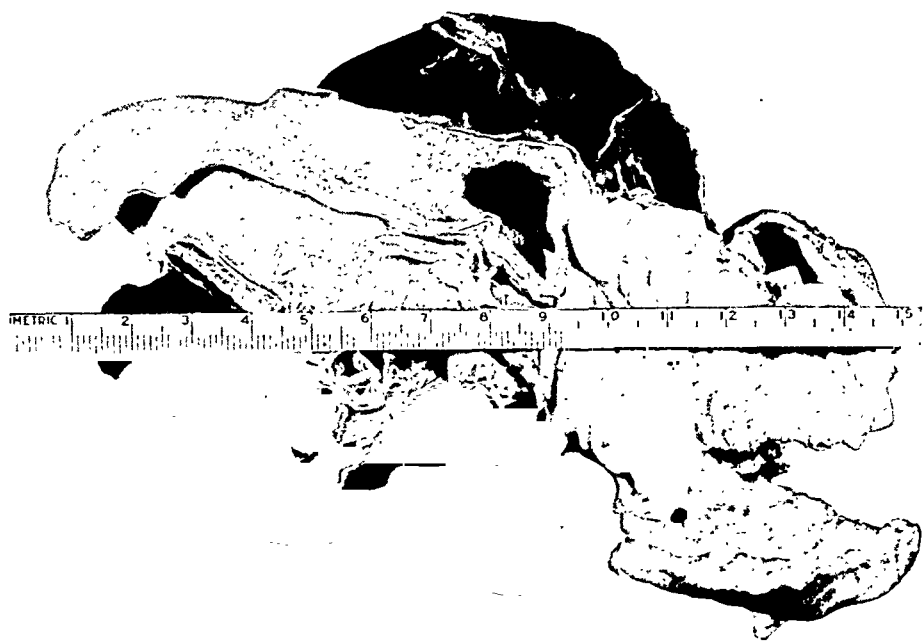


Fig. 6.—Stomach, duodenum and liver one hundred and sixty-eight days after ligation of the common bile duct and removal of 35 per cent of the liver. The animal died following a massive hemorrhage from the base of the large duodenal ulcer which had also eroded into the liver.



Fig. 7.—Pylorus and duodenum showing a large chronic duodenal ulcer two hundred and thirty-five days after ligation of the common bile duct. Marked cholangitis was also present.



Fig. 8.—Section of duodenal ulcer occurring in a dog ninety-three days after ligation of the common bile duct; reduced from a magnification of $\times 10$.

marily responsible for both, but the specific cause has not been demonstrated. With reference to obstructive jaundice in man, it should be noted that few human beings have complete biliary obstruction for more than a few months, and we have had a number of dogs with complete obstruction for almost a year without the development of peptic ulcer. If the difference in the vital span of these two species is considered, unrelieved jaundice would have to be present for a long time in the human being to be comparable with that in the animals under consideration here (figs. 1 to 8).

SUMMARY

Following ligation of the common bile duct there is marked decrease in resistance to the formation of peptic ulcer in dogs. In sixty-four animals, acute, subacute or chronic duodenal or gastric ulcers developed in from five to two hundred and ninety-five days after operation. Only twenty-three animals with uncomplicated complete obstructive jaundice, living from twenty-two to one hundred and ninety-five days, died of causes referable to ligation of the common bile duct without showing gross evidence of peptic ulcer.

TRAUMATIC NECROSIS OF THE LIVER WITH EXTENSIVE RETENTION OF CREATININE AND HIGH GRADE NEPHROSIS *

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The possible relationship between the concurrence of a liver severely damaged by trauma and a high grade nephrosis with extreme retention of creatinine leads us to a consideration of the mechanism by which such a picture might be produced. We could find a record of but one case that in any manner paralleled the one reported here.

REPORT OF A CASE

History.—H. C., a white boy, aged 15, was admitted to St. Luke's Hospital on June 20, 1930, and died on July 1, 1930. He was injured when an automobile turned over and a portion of the car rested on his chest and abdomen.

When he entered the hospital, he was in a state of shock. Examination revealed an abrasion on the left thoracic wall, fracture of the right clavicle, subcutaneous emphysema above and below the right clavicle and tenderness along the right costal margin and in the region of the right kidney. No abdominal rigidity was present. The temperature was 96 F. and the pulse rate, 120. On the day of admission the temperature rose to 102.8 F. and returned to normal within two days. The day before death it again rose to 101 F. Roentgen examination revealed fractures of the right clavicle and the right fifth, sixth and seventh ribs. A catheterized specimen of urine showed a few red blood cells and albumin. This finding continued throughout the illness. The patient vomited whenever water was taken by mouth. On the second day after admission he complained of abdominal soreness, and the tenderness along the right costal margin and in the region of the kidney increased; definite jaundice also appeared. On the fifth day fluid could be demonstrated in the abdominal cavity. It was thought that the gallbladder probably was ruptured.

On the sixth day, an exploratory laparotomy was done. An incision was made in the upper right rectus muscle with the patient under local anesthesia. The gallbladder was found intact. The abdominal cavity was filled with bloody, bile-stained liquid. Drainage was instituted, and the wound was closed without further exploration. The general condition of the patient was critical.

When the patient was admitted to the hospital, the blood pressure was subnormal. During the illness it gradually rose until it reached 150 systolic and 80 diastolic before death. The blood count showed secondary anemia and slight leukocytosis. During the first six days of the illness, the patient was given large quantities of 10 per cent dextrose intravenously and physiologic solution of sodium chloride. The latter, however, was reduced because of the suppression of urine. At no time during the illness did the patient pass more than 200 cc. of urine a day. Generalized edema developed. Vomiting continued daily during the entire

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* From the Departments of Surgery and Pathology, St. Luke's Hospital.

illness. The jaundice, which developed on the second day, continued until death. The patient died on the eleventh day following injury. He was conscious until the last two days.

The results of the chemical examination of the blood and urine are recorded in tables 1 and 2.

Necropsy.—The body was that of a large, well nourished boy. It measured 6 feet (182.9 cm.) in length and weighed 185 pounds (83.9 Kg.). The most striking feature on external inspection was the extreme degree of jaundice affecting the skin, sclera and mucous membranes. A low grade generalized edema was also present. A superficial cutaneous abrasion was seen over the fractured right clavicle. The latter crepitated readily on manipulation and when, on exploration, we found the fracture surrounded by a wide zone of both old and fresh hemorrhage. An abdominal incision, partly healed and sutured, was present in the

TABLE 1.—*Chemical Analysis of the Blood*

Date	Nonprotein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Whole Blood Chlorides, Mg. per 100 Cc.
6/22/30.....	75	3.7	106	440
6/23/30.....	120	6.0	114	495
6/24/30.....	150	13.0	101	500
6/25/30.....	150	14.0
6/26/30.....	146	18.0
6/28/30.....	200	22.0	121	515
6/29/30*.....	240	25.0
6/30/30.....	240	25.0	...	500

* The carbon dioxide combining-power of the blood plasma was 24 per cent by volume.

TABLE 2.—*Chemical Analysis of the Urine*

Date	Total Nitrogen, Gm. per 100 Cc.	Urea, Gm. per 100 Cc.	Urea Nitrogen, Gm. per 100 Cc.	Chlorides, Gm. per 100 Cc.	Total Urine in 24 Hours, Cc.
6/27/30.....	0.613	2.88	0.575	125
6/28/30.....	0.583	0.988	0.462	0.44	110
6/29/30.....	0.491	1.44	0.57	175
6/30/30.....	0.8	1.6	0.7	0.736	160

region of the right rectus muscle in the upper part of the abdomen. This incision held three rubber drains.

The peritoneal cavity contained about 2 liters of bright red, very bloody fluid without clots. The liver was somewhat enlarged, weighing 2,330 Gm. and measuring 29 by 20 by 10 cm. It was greenish brown. On the upper surface of the right lobe immediately under the diaphragm, there was a laceration of Glisson's capsule about 5 cm. in length, which was spread apart about 2 cm., revealing the substance of the liver beneath. In the midline, between the right and left lobes on the anterior surface, there was a discolored, reddish mottled, elongated area, which was slightly depressed. This irregular band of discoloration varied from 2 to 4.5 cm. in diameter and extended along almost the entire anterior superior exposed surface out to the free margin. The hepatic tissue beneath this band was softer in consistency than that adjacent to it, and when sectioned it was soft, hemorrhagic and pulpified. The capsule over it was not ruptured.

On cross-section, this pulpified hepatic tissue was found to extend over an area roughly approximating the size of the clenched fist. It was so located as to include the larger proximal ramifications of the right and left hepatic ducts. In the tissue

not involved in the pulpification, the bile ducts were considerably dilated, and the parenchyma of the liver was pigmented with bile. When the extrahepatic ducts were traced into the liver, we found the traumatized area to extend within about 2 cm. of their entrance into the substance of the liver.

An incidental finding was a cavernous hemangioma about 4 cm. in diameter extending into the liver like a wedge on the free edge anteriorly, about 5 cm. lateral to the midline and entirely outside the traumatized zone.

The gallbladder was somewhat distended with thick, black, viscid bile which could be forced into the duodenum through the papilla of Vater only when great pressure was exerted. The mucosa of the duodenum was edematous and deep yellow. The remainder of the small intestine showed nothing but a few subserous petechiae. In the large intestine both submucous and subserous hemorrhages were diffusely distributed, some of them measuring as much as 1 cm. in diameter.

The kidneys were greatly swollen and softened, and of about equal size. They weighed together 580 Gm. When sectioned, the capsules retracted and stripped easily, revealing a dark greenish-red, mottled, cortical surface. The outlines between the medulla and cortex were distinct, owing to a rather intense hyperemia of the pyramids. The cortex had a swollen lusterless appearance suggesting a high grade degenerative change. The blood vessels showed no emboli or thrombi, and the ureters and bladder were essentially normal.

Both pleural cavities contained about 250 cc. of bright red, unclotted, very bloody fluid, and the lungs were partially collapsed. In both lungs interstitial, parenchymatous and subpleural hemorrhages were seen, some measuring as much as 15 mm. in diameter. No areas of pneumonia were found. The right fifth, sixth and seventh ribs were fractured, but had not penetrated the parietal pleura.

Aside from the extreme pigmentation of the bile of all the viscera, no other noteworthy findings were encountered.

Histologic Pathology.—Heart: The myocardial fibers showed some swelling and considerable fragmentation and segmentation. The epicardial mesothelial cells were almost cuboidal and showed some proliferation. There was some accumulation of green pigment in most of the cells.

Lungs: Many deeply pigmented cells were found in the alveoli which were probably exfoliated, alveolar epithelial cells. Masses of red cells, sometimes intermingled with stringy, fibrinous material, were seen in many of the alveoli, but no exudate of pus cells was present.

Liver: Glisson's capsule was intact. It showed some pigmentation with bile. The lobulation of the nontraumatized area was fairly distinct. About the central veins the hepatic cells showed some shrinkage and cytoplasmic granulation. Between many of the cells in this region of the lobule the biliary canaliculi and capillaries were plugged with bright green pigmented material which was not actually seen in the liver cells but was found at the points where the fine capillary twiglets entered, and where they ran between the cells. The stellate cells of Kupffer were swollen, and many of them contained some greenish, granular pigment. Many were partially torn away from the columns of hepatic cells and seemed to be desquamated into the sinusoids.

In the pulpified region, we saw large areas of hemorrhage in which no viable hepatic cells were present. Dead, non-nucleated, amorphous shadows, staining faintly eosinophilic and presenting the typical outline of parenchymatous cells of the liver, were found in masses scattered about in these hemorrhagic areas. In some respects these zones resembled those seen in eclampsia. The areas were surrounded by a thick zone of fibroblastic appearing cells in which proliferating bile ducts were numerous, and occasional disintegrating hepatic cells were seen. The fibroblastic cells were growing into these areas of hemorrhage. Peripheral

to these fibroblastic zones, the parenchyma of the liver resembled the remainder of the liver previously described.

Spleen: The capsule showed some greenish pigmentation, and considerable green granular pigment was scattered about in the pulp. Red cells were only infrequently encountered here, and then they appeared as mere faintly pigmented, pale shadows. Scattered eosinophils were seen in the pulp. The malpighian bodies were not distinctly outlined.

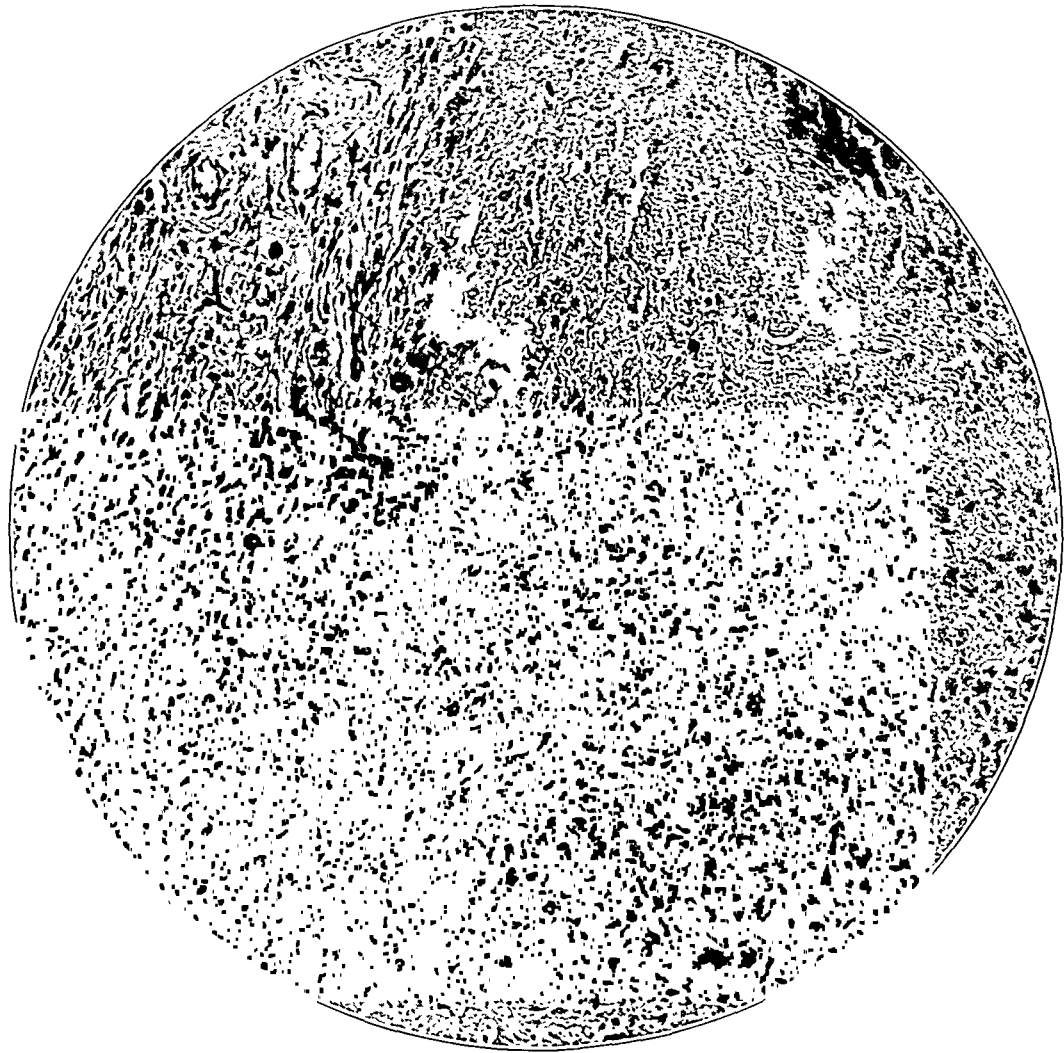


Fig. 1.—Low power photomicrograph of the liver showing the border of the area of hemorrhagic, necrotic pulpification. The upper left portion shows the fibroblastic zone with organization; the extreme right side, necrotic hepatic cells; the center, predominant hemorrhage; $\times 125$.

Pancreas: The pancreas was histologically normal.

Gastro-Intestinal Tract: The duodenum in the region of the papilla of Vater showed a swollen mucosa and submucosa. The epithelium lining the villi was almost entirely exfoliated, and the submucosa looked dead. It was anuclear and pigmented a diffuse greenish hue. The hemorrhagic areas in the small and

large intestine showed desquamation and granular disintegration of the epithelium, and in the epithelial stroma rather extensive focal hemorrhages were present.

Kidneys: In the medullary portion scattered foci of leukocytes were seen. Monocytes, plasma cells and eosinophils were present in large numbers. Here the substance of the kidney seemed to be completely disorganized, and some fibroblasts were seen in these irregular focal leukocytic accumulations. Some scattered interstitial hemorrhages were also encountered, and many of the small ves-

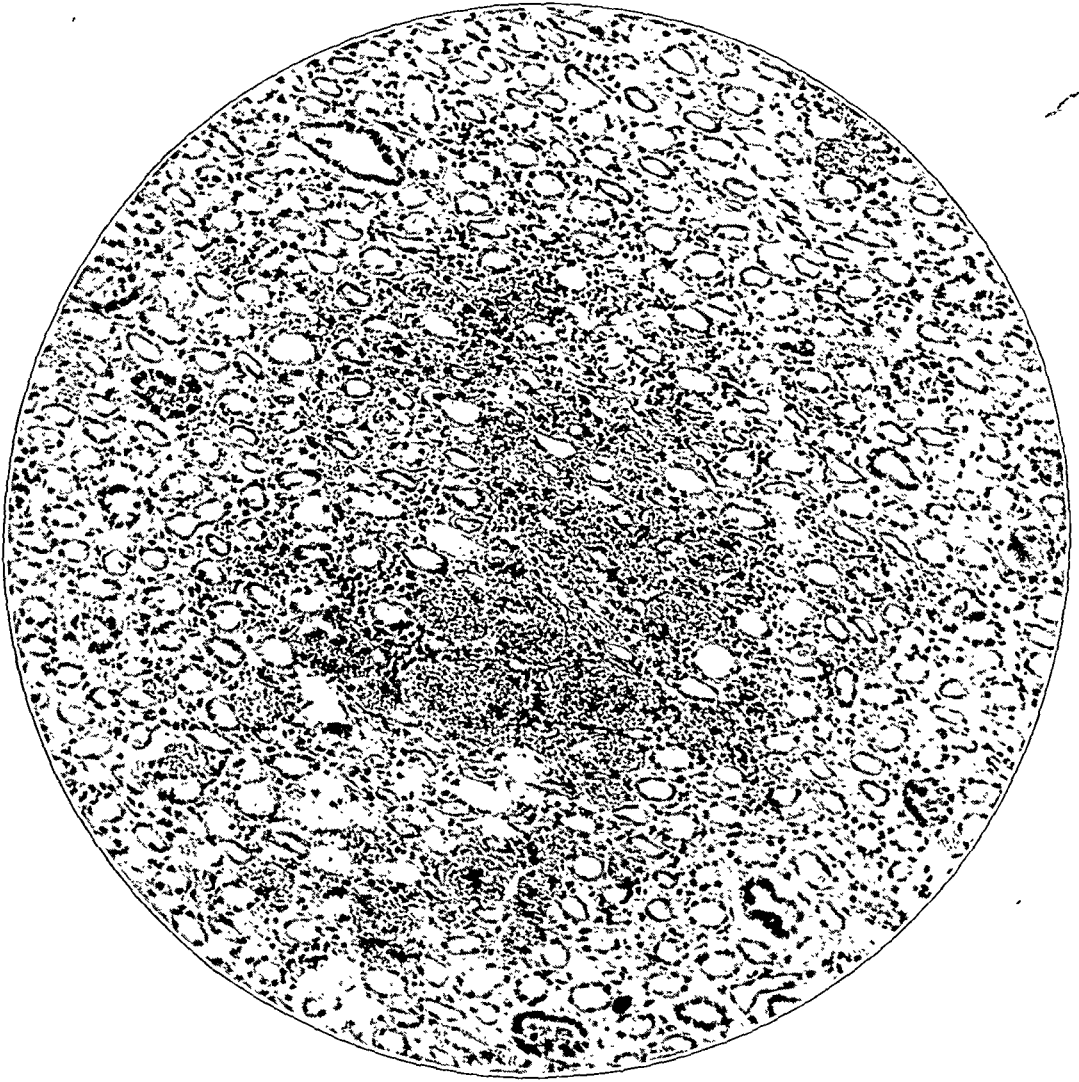


Fig. 2.—Low power photomicrograph of the kidney showing vascular congestion, hemorrhage and interstitial leukocytic reaction secondary to degenerative changes; $\times 125$.

sels and capillaries were widely dilated with red cells; some of the latter appeared to be undergoing hemolysis. Many of the tubuli of the medulla also contained red cells. In addition to cloudy swelling, a granular, albuminous precipitate and pale casts were found in the collecting tubules. Some of the latter showed regeneration of the epithelium. In the cortex, the convoluted tubules and loops of Henle showed an extensive parenchymatous degeneration. Many tubules were seen in which the epithelial cells contained only two or possibly three nuclei; these

nuclei were pale and hazy and apparently undergoing karyolysis. Some tubules contained no nuclei and seemed to have undergone complete necrosis. The cytoplasm of the epithelium of the more highly differentiated tubules was generally pigmented with greenish, fine, dusty granules. The glomeruli showed swelling of the epithelium lining Bowman's capsule, and there were red cells scattered about in the space between the tuft and the capsule. In the capillary loops the endothelium was somewhat swollen and a few polymorphonuclear leukocytes were seen here and there in the tortuous capillary channels.

Special fat stains used on sections from both kidneys showed no evidence of fatty degeneration or fat embolism.

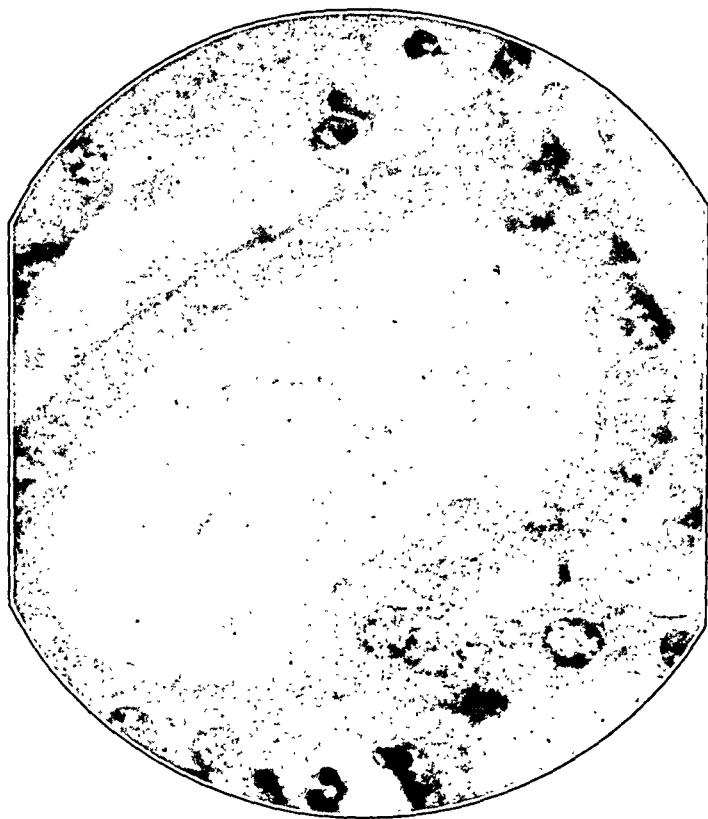


Fig. 3.—Oil immersion photomicrograph showing cortical renal tubule with absence of nuclei, nuclear shadows, karyolysis of the remaining swollen nuclei and stringy precipitate of albumin in the tubular lumen; $\times 500$.

COMMENT

In 1927, Furtwaengler,¹ from Professor Clairmont's clinic in Zurich, reported the case of a woman, 22 years old, who suffered a crushing injury to the liver in an automobile accident. She lived only three days, and in this period presented a clinical course almost identical with that of our patient, with the exception that she was not jaundiced. At necropsy a bilateral necrosis of the cortices of both kidneys was found.

1. Furtwaengler, A.: Diffuse Rindennekrose beider Nieren nach Leberruptur, *Krankheitsforschung* 4:349, 1927.

Furtwaengler believed that this patient had a latent tendency to vascular spasm due to some nervous disposition and that the cortical renal necrosis resulted from an ischemia produced by a hypothetical chemical toxin circulating in the blood, which toxin arose from decomposition of hepatic tissue. The toxin thus caused the vascular spasm which was followed by ischemia and subsequent renal necrosis. Among other possibilities that he ruled out were fat embolism and bilateral thrombosis or embolism of the renal veins or arteries.

Our case differs from Furtwaengler's only in degree. Careful histologic examination of the kidney showed both inflammatory and degenerative changes. This degeneration had proceeded to actual tubular epithelial necrosis in many of the more highly differentiated tubules, but was not so advanced as that described by Furtwaengler.

A certain degree of renal change might be explained on the basis of extensive jaundice with the bile acting as a poison to the renal epithelium. Dead hepatic tissue might also have produced some toxin which, when absorbed, acted on the kidney. In our case the jaundice was not wholly obstructive, since the stools remained colored up to the time when the patient began to bleed from the serous and mucous surfaces. There was, however, in the liver some degree of biliary obstruction from pressure of the pulpified hepatic tissue and hemorrhage on the larger hepatic radicles. Histologic examination of the liver showed a considerable degree of plugging of the biliary canaliculi. The marked degree of jaundice in our case and the possible decrease in the ability of the liver to excrete fibrinogen might account for the extensive bleeding in the latter period of the patient's illness. Moreover, some of the jaundice could possibly have resulted from the severe bleeding with absorption of hemoglobin derivatives.

The extreme retention of creatinine was distinctly out of proportion to the retention of other nitrogenous products. Although the terminal figures for nonprotein nitrogen were high, these values were in no way comparable to the remarkable rise of creatinine in the blood to 25 mg. per hundred cubic centimeters. The marked decrease in nitrogen in the urine was striking, although it was about what might be expected in a person in whom the retention of nitrogen in the blood was so high and the urinary output so scanty.

There is yet another action that may arise from biliary obstruction which could have been present in our case, namely, the elaboration of an active vasodepressor substance in the liver. After tying the common bile ducts of dogs, Radvin² obtained from their livers an extract containing both histamine and choline which was a potent vasodepressor.

2. Ravdin, I. S.: Vasodepressor Substances in the Liver After Obstruction of the Common Duct, *Arch. Surg.* **18**:2191 (May) 1929.

Recently McEnery, Myer and Ivy,³ through the production of mechanical ischemia of the kidney, were able, in a short period, to cause a condition in dogs clinically simulating uremia, from which the animals died. Scriver and Oertel⁴ in a discussion of necrotic sequestration of the kidney in pregnancy, explained their findings on the basis of a vasoparalysis with subsequent thrombosis. Beneke and Schmorl⁵ on the other hand, felt that the necrotic changes seen in the so-called "pregnancy kidney" of eclampsia were due to some pressor substance elaborated by the liver and producing vascular spasm, ischemia and subsequent necrosis. Moreover, such observers as Griesinger and Leyden⁶ held that the necrosis seen in the kidney in cholera was due to vascular spasm and ischemia. However, Fraenkel⁷ explained this necrosis of the kidney as being due to the direct action of the cholera toxin. Scriver and Oertel⁴ believed that the idea of vascular spasm and ischemia, as well as "the rather hazy theories of primary toxic cell degeneration," does not explain the changes in the kidney as logically as their own hypothesis of vasoparalysis.

Just what the relationship between the kidney and the liver may be is not definitely understood. The apparent adverse effects of disease of the hepatic and biliary tract on the kidney have been noted by such authors as Fitz-Hugh⁶ and Zaffagnini,⁷ and the harmful effect on the kidney seen in some cases of obstruction of the common bile duct is a well recognized fact. We have seen a patient with a previously undamaged kidney who died from uremia with extensive intestinal hemorrhage several days after a cholecystectomy was performed for removal of a stone. The liver showed a moderately severe hepatitis, and the renal changes were remarkably similar to those in the case presented here. Walters and Parham,⁸ in a case of obstruction of the common bile duct without operation, saw extensive intestinal hemorrhage and death from uremia. The exact mechanism of this renal damage is not clearly understood.

In our case several possibilities are present that might be considered of etiologic importance; all of them may have been of some impor-

3. McEnery, E. T.; Myer, J., and Ivy, A. C.: Studies on Nephritis, *J. Lab. & Clin. Med.* **12**:349, 1927.

4. Scriver, W. de M., and Oertel, H.: Necrotic Sequestration of the Kidneys in Pregnancy, *J. Path. & Bact.* **33**:1071, 1930.

5. Beneke, Schmorl, Griesinger, Leyden, Fraenkel, Gerhardt and Ogata, quoted by Kaufmann: Pathology for Students and Practitioners, authorized translation, Stanley P. Reimann, Philadelphia, P. Blakiston & Son, 1929.

6. Fitz-Hugh, Thomas, Jr.: Hepato-Urologic Syndromes, *M. Clin. North America* **12**:1101, 1929.

7. Zaffagnini, A.: Hematuria and Gallstones, *Arch. ital. di urol.* **4**:161 (Dec.) 1927.

8. Walters, W., and Parham, D.: Renal and Hepatic Insufficiency in Obstructive Jaundice, *Surg., Gynec. & Obst.* **35**:605, 1922.

tance in producing the complete pathologic picture. We must consider the pulpified, necrotic liver as possibly elaborating some toxin which, through the blood, acted on the kidney or its blood supply. We must also consider the jaundice that appeared early in the disease and increased progressively until death. And we must not disregard traumatic shock and trauma to the kidney itself. Regarding the last factor, it might be mentioned that no evidence of trauma was found at necropsy, although the patient had blood in the urine at the first examination. Trauma alone has been considered by Neubürger⁹ to be the cause of an angiospasm of the renal artery of sufficient intensity to cause ischemic infarction without thrombosis in several cases that he has investigated.

As regards jaundice, the picture produced in our case was not that usually found in necrosis caused by bile. Although the kidney was pigmented, the typical "grass-green kidney" was not seen. However, we do know that bile acting on the protoplasm of the more highly differentiated epithelium of the kidney, particularly the convoluted tubuli, leads at times to actual epithelial necrosis (Gerhardt and Ogata⁵).

The multiple factors in our case somewhat clouded the development of the picture. However, we feel that, in the absence of thrombosis, neither vasoparalysis nor vasoconstriction alone could have caused the renal picture. It seems more logical to assume that some potent toxin was produced in the liver from hemorrhagic necrosis which acted directly on the parenchymatous cells of the kidney, since the histologic picture produced was that of a slow degenerative change proceeding to necrosis with the superimposed inflammatory reaction secondary to the degenerative change. Many of the tubules in the kidney showed only cloudy swelling, while others had lost their nuclei by karyolysis, and not infrequently nuclei were seen in an incomplete stage of autolysis.

CONCLUSIONS

A case of traumatic pulpification of the liver without rupture is reported in which the patient died after eleven days, with an extensive nephrosis. He was extremely jaundiced and had diffuse hemorrhages into the serous cavities. The output of urine was scanty, and the blood nitrogen was greatly increased, particularly the creatinine, which amounted to 25 mg. per hundred cubic centimeters. The mechanism of renal necrosis is discussed, and the histologic renal picture, as well as the clinical course, would seem to favor the theory that some toxin was elaborated in the liver through hemorrhagic necrosis which acted directly on the kidney.

9. Neubürger, K.: Angiospasm as a Cause of Renal Infarcts, *Virchows Arch. f. path. Anat.* **265**:789, 1927.

CANCER AND WEIGHT*

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The influence of diet on cancer has been intensively studied for the last twenty years by means of experimentation on animals. As a result of this study, it may be stated that either certain vitamin deficiencies or low caloric diets will delay or prevent the taking of transplants of nearly all the transplantable tumors. On the other hand, dieting after the implant is established has no effect on many tumors, and a comparatively insignificant one on others. Tumors may stop growing when abnormal diets are used, but the animals seldom survive any longer than those on a normal diet and are never cured by such means. Much of the recent work in this field is referred to in an article by Henry Jackson, Jr.¹

In the clinics, little attention has been paid to diet in cases of cancer, and no well controlled experiments have been recorded in the literature that indicate any worth while results from dietary treatment. For centuries, there have been sporadic developments of starvation or other dietary treatment, but none of them have lasted long or been taken up widely.

If diet does not influence the cure of cancer, there are, however, some data at hand that indicate a possible relationship between bodily nutrition and the etiology of cancer. In Hoffman's² book may be found some figures that show that people who are overweight when they take out life insurance are more liable to die from cancer than people who are of normal weight. People who are underweight have a reduced liability. Further work on this subject has been done by Dublin and Jackson and is published in Jackson's³ paper. Their figures show an increased liability to death from cancer of nearly 50 per cent in obese persons as compared with those who are underweight. It is interesting that figures compiled from such data should be of any value, because the time elapsing between the weighing of the person until death from cancer must average from twenty to thirty years, and in many cases be well over fifty years.

* Submitted for publication, April 13, 1931.

* From the Huntington Memorial Hospital and Department of Surgery, Harvard Medical School. This work was supported by an anonymous gift to the Harvard Medical School.

1. Jackson, Henry, Jr.: Recent Advances in the Biology of Cancer, New England J. Med. **201**:294, 1929.

2. Hoffman, F. L.: The Mortality of Cancer Throughout the World, Newark, N. J., Prudential Press, 1915.

3. Jackson, D. L.: Carbohydrate Metabolism in Cancer, Texas State J. Med. **24**:622, 1929.

Another aspect of this general problem, and one that it is possible to study from data in the hospital records, is to determine whether there is a relationship between the patient's weight and the prognosis of the disease. This, of course, is quite different from trying to obtain a cure by diet or to show that there is a relation between weight and incidence.

METHOD OF STUDY

It seemed well to start the study with single clinical and pathologic entities in which a single form of treatment was used. At the Huntington Hospital, cases of carcinoma of the cervix and of the uterus are most suitable for study with respect to many factors. Dr. George A. Leland has had patients with these conditions under his care since 1920, and those with carcinoma of the cervix have been treated with radium rather than by surgical measures or mixed treatment. He has just completed a thorough survey of these cases from the opening of the hospital through the year 1924, and the percentage in which there was a complete five year follow-up is high. Beginning in 1920, a record of the patient's weight may be found in most instances. Therefore, this study was limited to the five year period from 1920 to 1924. Unfortunately, no records were made of the patient's height, so that conclusions as to the degree of obesity of a given patient cannot be drawn too accurately.

In preparing the tables, the following standards of suitability were followed:

1. Presence of clinical carcinoma of the cervix or of the uterus, proved by pathologic examination, at the time of the first treatment with radium.
2. Record of the patient's weight on first entry.
3. Known survival for five years or death from clinical cancer in less than five years.
4. Treatment with radium.⁴
5. No subsequent radical operation.

In order to adhere strictly to these standards, it was necessary to eliminate about half of the cases with a diagnosis of carcinoma of the cervix or of the uterus, according to the files in the hospital. These eliminations were made largely for three reasons, in the following order of frequency: (1) no record of weight; (2) no pathologic report or (3) patient lost from observation. (There were only twenty-four cases lost from observation that were otherwise suitable.) The cases without record of weight or those that were not followed could not be used.

The satisfactory cases were separated into two groups and each studied separately. These groups consist of two distinct pathologic enti-

4. The methods of treatment used may be found in G. A. Leland's "Radium Treatment in Cancer of the Female Pelvis" (*Physical Therap.* 48:281 [June] 1930).

ties: (1) epidermoid carcinoma of the cervix (475 cases) and (2) adenocarcinoma of the cervix and of the uterus (79 cases). Cases of adeno-acanthoma, carcinoma simplex or colloid carcinoma were not included in any group. There were only 15 of these, and in all the outcome was fatal.

Patients surviving five years were arbitrarily considered as cured. These patients were again classified as to the results after the five year period (column *L* on the charts) as follows: (1) those who died from carcinoma or were alive but diseased and (2) those who were living and not diseased or who had died from other causes.

EPIDERMOID CANCER OF CERVIX

Relation of Weight to Survival.—From the total of over 900 cases of epidermoid carcinoma of the cervix, 475 were suitable for study.

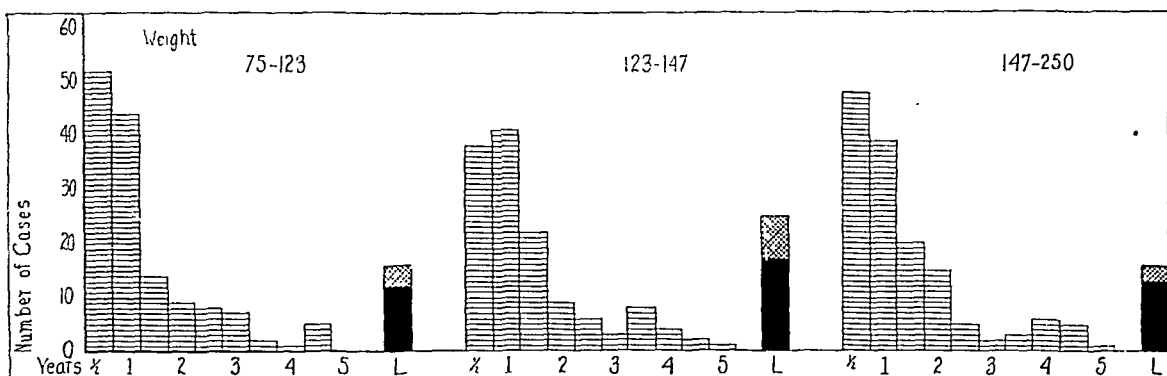


Chart 1.—Length of survival in six month periods of 475 persons with epidermoid carcinoma of the cervix. The patients are divided into three equal groups according to weight. In this and the following charts, the area composed of straight lines indicates those patients who died in less than five years; the crossed area, those who died from the disease or were alive and diseased after the five year period; the black area, those who were alive and well or who died from causes other than the disease after the five year period.

These were tabulated and divided in various ways according to weight. Whatever the method of division, the same general tendency will be seen.

Chart 1 shows the length of survival in six month periods in the cases divided into three equal groups according to weight.

Chart 2 is similar, showing the cases divided into five equal groups. It will be seen at once that the proportion of cases in which the patients survived five years is much higher among those of normal weight than among those whose weight was above or below normal.

Results shown in the foregoing manner would be difficult to compare with results from other clinics or from other groups of cases in our clinic because the points of division of other cases into equal fifths or

equal thirds might not correspond to these. The same cases are therefore presented in another manner in table 1. Here the cases are divided according to weight; 20 pound (9 Kg.) intervals are used in the groups from 75 to 174 pounds (34 to 78.9 Kg.), while weights above 174 pounds are included in a single group. In this table the time of survival of patients who did not live for five years is omitted, and only the total number of cases, the number of survivals and percentage of survivals are presented. Again, however, the survivals are subdivided into two

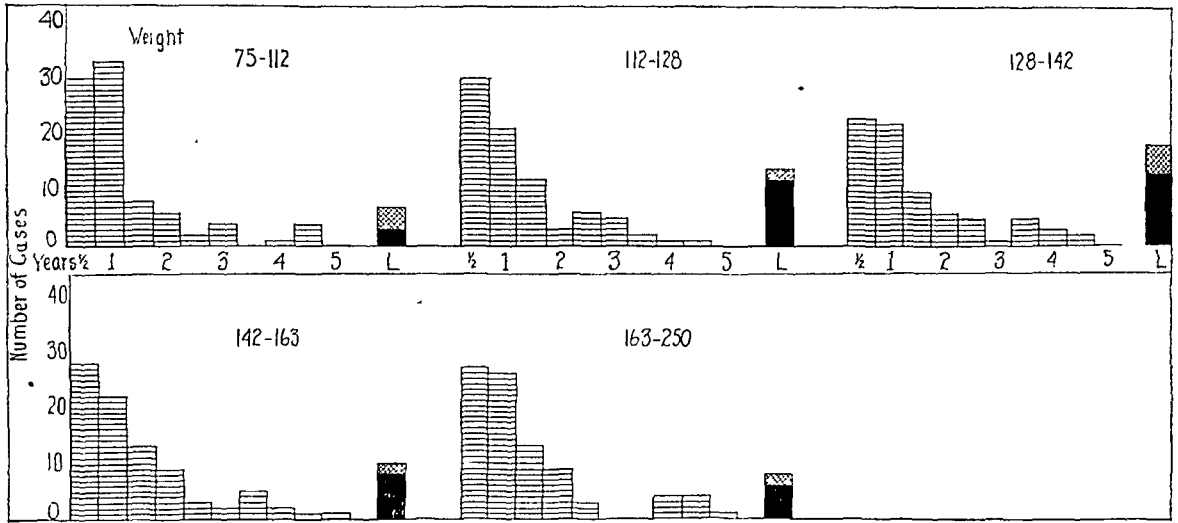


Chart 2.—Same as chart 1, except that the cases are divided into five equal groups.

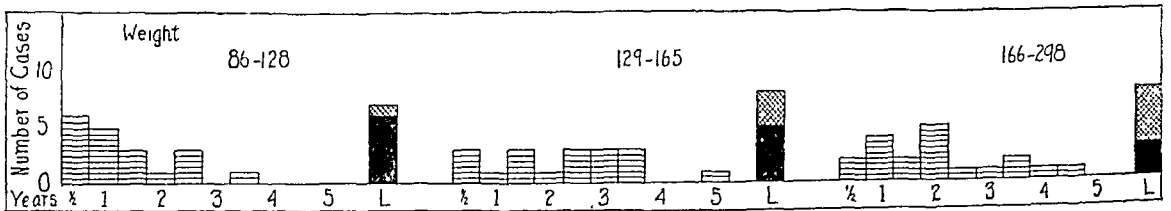


Chart 3.—Length of survival in seventy-nine persons with adenocarcinoma of the cervix.

classes as previously. The apparent discrepancies between this table and the preceding charts will be discussed later.

ADENOCARCINOMA OF THE CERVIX AND FUNDUS

For the purpose of this study the cases of adenocarcinoma of the cervix and of the fundus were grouped together. This does not mean necessarily that a single pathologic entity is being dealt with, but it was done purely for practical reasons. The first reason is that either group alone is too small to be at all significant statistically; the second, that it is not always possible to tell from the record whether the disease orig-

inated in one or the other part of the uterus. There were 39 cases of adenocarcinoma of the cervix and 40 cases of adenocarcinoma of the fundus. Chart 3 shows the 79 cases divided into thirds and presented in the same form in which chart 1 presents the cases of epidermoid carcinoma. It will be seen at once that the median weight in these cases

TABLE 1.—*Data on Four Hundred and Seventy-Five Cases of Epidermoid Carcinoma of the Cervix**

Weight, Pounds	Number of Cases	5 Year Survival With Disease		5 Year Survival Without Disease		Total 5 Year Survival	
		Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
75-94	21	1	5.0	1	5.0
95-114	90	3	3.3	6	6.6	9	10.0
115-134	127	2	1.5	14	11.0	16	12.5
135-154	113	6	5.0	11	10.0	17	15.0
155-174	59	3	5.0	7	12.0	10	17.0
175+	65	4	6.0	4	6.0

* These cases are divided into groups with weight divisions of 20 pounds each.

TABLE 2.—*Data on Seventy-Nine Cases of Adenocarcinoma of the Cervix and of the Uterus**

Weight, Pounds	Number of Cases	5 Year Survival With Disease		5 Year Survival Without Disease		Total 5 Year Survival	
		Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
75-123	21	4	19.0	4	19
123-147	21	2	9.0	5	24.0	7	33
147+	37	7	18.5	5	13.5	12	32

* These cases are divided into three groups corresponding to the weights at which the epidermoid groups were divided into equal thirds in chart 1.

TABLE 3.—*Data on Seventy-Nine Cases of Adenocarcinoma of the Cervix and Uterus**

Weight, Pounds	Number of Cases	5 Year Survival With Disease		5 Year Survival Without Disease		Total 5 Year Survival	
		Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
75-94	1	1	100	1	100
95-114	13	2	15	2	15
115-134	19	1	5	3	16	4	21
135-154	14	2	14	3	21	5	35
155-174	9	1	11	2	22	3	33
175+	23	5	21	3	13	8	35

* These cases are divided by weight into groups at 20 pound intervals.

is much higher than in the group of epidermoid carcinoma, and that, therefore, the dividing line between the upper and middle groups is 18 pounds (8.2 Kg.) higher. Therefore, table 2 has been made up to show a division in these cases at the same weights at which the cases of epidermoid carcinoma were divided.

Table 3 represents another tabulation of these cases and is made on exactly the same basis as table 1. The cases are listed in 20 pound divisions.

COMMENT

Statistics.—In work of this type it is fundamental to know whether there is any possibility that the statistics presented actually show what they appear to demonstrate. Fallacious findings may be due to accidental or systematic sources of error. By the former are meant especially errors due purely to chance. This type of error is gradually reduced as the series increases in size. Dr. E. B. Wilson informed me that a series of cases in which 57 are differentiated from a group of 475 and then systematically divided into from three to five groups is large enough to make the possibility of error due to chance very small. On the other hand, the second group presented, the adenocarcinomas, is so small that chance can easily account for the apparent differences. Every effort was made to eliminate systematic errors by rigidity in the selection of cases, so that selection was purely automatic on the basis of the records. None of the cases have ever been seen by me. As a partial check on the work, a group of cases was reviewed that was eliminated from the preceding tables for causes other than that the patient was lost from observation, there was no record of weight or that treatment had not been given. These cases included those in which the patients showed clinical cancer, but no pathologic report had been made, cases in which the patients had been operated on elsewhere and positive pathologic reports made, after which they were sent to this hospital for prophylactic radiation, and cases in which the patients had had radical operations performed elsewhere after receiving treatment with radium in this hospital. There were 78 of these cases, tabulation of which showed exactly the same tendency toward the grouping of cures in the patients of middle weight as in the proved cases of epidermoid carcinoma. This checks against the possibility that these eliminations changed the results in any way.

Epidermoid Carcinoma of the Cervix.—Whether these cases are presented in the form of a division into equal thirds, equal fifths or unequal division according to 20 pound intervals, it is definitely shown that the greatest percentage of cures occurred in the patients who were of middle weight.

An apparent discrepancy between the results in chart 2 and in table 1 lies in the fact that the greatest percentage of cures occurs at different points, higher in table 1 than in chart 2. Which form of presentation gives the truest picture cannot be stated.

Whatever form is used for tabulation, there is no doubt that the prognosis is more favorable for the more normal patients than for the fat or the thin ones. The obvious explanation for the unfavorable prognosis in the cases in which the patients are very thin is the increased proportion of patients who have lost weight and are in the terminal stages of the disease. This I believe to be true and shall not discuss further.

The reasons for the poor results in fat patients are, however, not so obvious. One factor probably is the purely mechanical difficulty of applying radium accurately. In making any explanations beyond this, one has to enter the realms of pure speculation. Does the fat person have less resistance, or does the malignant condition find a more fertile field for growth?

Adenocarcinoma of the Uterus and of the Cervix.—All three tabulations of these cases show approximately the same results, and results that are different from those shown for the cases of epidermoid carcinoma. If the patients who survived for five years are considered as a whole, there is no difference in the groups of different weights. It is striking, however, that in the group of patients who were overweight so many who were considered cured were alive and diseased or were dead from the disease after the five year period that the patients actually alive and well for more than five years were hardly 50 per cent of the corresponding number in the patients who were of middle weight.

The series of patients with adenocarcinoma is so small that these findings may be entirely fallacious for this reason alone. Another reason why these cases cannot be compared with those of epidermoid carcinoma of the cervix has to do with the indications for treatment. In the latter group, radium was used in all cases no matter how favorable the condition was for operation. On the other hand, half of the cases of adenocarcinoma were of the fundus. If the disease was not too extensive and the patients were otherwise in good condition, they were operated on and are therefore ineligible for this series. Obesity was, however, the most common contraindication to operation in the less advanced cases of adenocarcinoma of the fundus. This basis of selection has led to two probable results: 1. The patients with adenocarcinoma are heavier as a group than those with epidermoid carcinoma. (Of course, adenocarcinoma may be a disease that occurs more frequently in heavy people, but this cannot be determined from any data available.) 2. In the majority of cases the adenocarcinomas were less advanced in obese persons than in thin persons or in those of moderate weight.

SUMMARY AND CONCLUSIONS

1. Study of 475 proved cases of epidermoid carcinoma of the cervix in which treatment with radium was used shows that the percentage of cures of patients with approximately normal weight was twice that of patients who were much over or much under normal weight.

2. A group of seventy-nine patients with adenocarcinoma of the cervix or fundus of the uterus was similarly studied, and a definite but less marked relationship of weight to prognosis was found.

EXPERIMENTAL ESOPHAGEAL OBSTRUCTION *

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AND

RALPH B. MULLENIX, M.S.

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As has been suggested by many workers, in cases of high intestinal obstruction there are two fairly well defined groups of factors that probably operate in the pathogenesis of the untoward symptoms that develop. Dehydration, with loss of chlorides and other constituents of gastro-intestinal and pancreatic secretions either by vomiting or by failure of reabsorption, on the one hand, and toxemia from the absorption of toxic substances from the intestinal lumen, on the other hand, may operate more or less independently at times, but probably more often concurrently and with a reciprocal influence in the usual case.

In an analysis of some of the factors concerned in intestinal obstruction, Haden and Orr,¹ in 1923, produced various types of experimental obstruction of the cardia and esophagus and reported that severe toxemia with rapid death resulted. They ascribed the symptoms and death to the same causes that were thought by them to be operative in obstruction of the gastro-intestinal tract at lower levels. Both the observations and the conclusion seemed to us to be difficult to explain. In the first place, it is well known that many patients survive obstructions of the esophagus either from stricture or from new growth without the development of fulminating symptoms related to the obstruction per se. In the second place, it is difficult to appreciate adequate mechanisms for either the loss of important gastro-intestinal secretions or the development of toxemia. Vomiting cannot occur, and it seems improbable that sufficient disturbance of the gastro-intestinal tract would develop to prevent reabsorption of the juices secreted. Similarly, the factors apparently necessary for the formation and absorption of toxic substances, such as distention, strangulation or impairment of the blood supply, are not established.

* Submitted for publication, May 15, 1931.

* From the Department of Physiology and Pharmacology, Northwestern University Medical School.

1. Haden, R. L., and Orr, T. G.: *Chemical Changes in the Blood of the Dog After Obstruction of the Esophagus and Cardiac End of the Stomach*, J. Exper. Med. **38**:477, 1923.

In 1930, Andrus and Donnelly² corroborated the observations of Haden and Orr that toxemia and rapid death result from obstruction of the esophagus. They offered the suggestion that the loss of saliva might play a rôle in the lethal outcome, apparently disregarding the fact that many laboratory workers have succeeded in keeping dogs alive with an esophageal fistula in the repetition of sham feeding experiments such as Pavlov originated. In 1928, Haden and Orr³ reported further experiments on obstruction of the cardia, in which they again emphasized the marked toxemia that develops. This belief was apparently concurred in by Wangenstein and Chunn,⁴ although they commented on the facts that vomiting could not occur and that the factor of absorption was reduced to a minimum.

Because of the seeming conflict between these reports and the clinical experience with esophageal obstruction, and because they seemed to nullify many of the arguments with respect to the interpretation of the pathogenesis of symptoms in acute intestinal obstruction, we were stimulated to perform a number of experiments on esophageal obstruction which we are reporting at this time. All the experiments were performed on dogs. The surgical procedures were carried out under aseptic precautions and under general anesthesia with either ether or pentobarbital sodium.

EXPERIMENTAL WORK

1. *Simple Obstruction by Means of a Ligature.*⁵—In ten dogs the esophagus was obstructed in the neck by means of a stout ligature. Six dogs died in twenty, thirty-three, thirty-six, forty, sixty and seventy-four hours, showing at autopsy well marked pneumonia. Four dogs died in sixty-four, sixty-five, seventy-four and eighty-four hours, showing at autopsy no pneumonia, but marked cervical cellulitis and mediastinitis, apparently due to cutting through of the ligature with consequent leakage. Blood chlorides were followed in all the dogs. In the group with pneumonia there was an average fall of 83 mg. per hundred cubic centimeters of blood. In the remaining four animals, there was an average fall of 32 mg.

2. Andrus, W. D., and Donnelly, J. L.: Effects of Certain Operations on the Esophagus of the Dog: Including Esophageal Obstruction and Complete Esophageal Fistula, *Arch. Surg.* **20**:1 (Jan.) 1930.

3. Haden, R. L., and Orr, T. G.: The Effect of Sodium Chloride on the Chemical Changes in the Blood of the Dog After Obstruction of the Cardiac End of the Stomach, *J. Exper. Med.* **48**:627, 1928.

4. Wangenstein, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction, *Arch. Surg.* **16**:1242 (June) 1928.

5. The experiments in this group were done by one of us (Dr. Dragstedt) and Dr. John F. Huffman during 1927 and 1928.

In five dogs the esophagus was obstructed in the chest about 4 cm. above the diaphragm by means of a stout ligature. Three dogs died in twenty-seven, thirty-six and thirty-nine hours, showing at autopsy well marked pneumonia. Two dogs died in forty-eight and seventy-two hours, showing mediastinitis apparently due to cutting through of the ligature with consequent leakage. In the group with pneumonia the average fall in blood chlorides was 50 mg. per hundred cubic centimeters of blood. In the other two animals there was no fall in blood chlorides. It is thus apparent that the fall in blood chlorides is not comparable to that seen in acute intestinal obstruction and is no greater, in our opinion, than can be accounted for by the pneumonia.⁶

2. *Closed Loop Obstruction of the Esophagus.*—Closed loops of the esophagus were made in six dogs by ligating the esophagus just above the diaphragm in the chest, sectioning the esophagus in the neck, inverting the lower end and bringing out the upper end through the incision as a fistula. The animals died in thirty, forty-eight, sixty, sixty, seventy-four and seventy-six hours. At autopsy, two showed cellulitis of the neck but no leakage from the loop. The remaining four all showed mediastinitis subsequent to distention of the loop and leakage from one or both ends. It was noted, however, that none of the dogs had pneumonia. The significance of this observation will be referred to later.

3. *Simple Obstruction of the Exteriorized Esophagus.*—As 60 per cent of the animals in group 1 showed pneumonia at autopsy and none of the animals in group 2 developed pneumonia, it seemed possible that the pneumonia in group 1 was due to aspiration, which was prevented from occurring in group 2 by having the distal end of the oral segment of the esophagus drained to the outside. As these operations were done in one stage under general anesthesia, it was desired to exclude the factor of anesthesia in the development of the pneumonia.

In ten dogs the esophagus was exteriorized in the neck by freeing it for a considerable distance and suturing the muscles and skin of the neck beneath it. The technic of the operation we have described elsewhere.⁷ Ten days later the exteriorized esophagus was simply obstructed by means of a ligature or a rubber-jawed clamp. In the five dogs with the ligature obstruction, immediate swallowing efforts with profuse salivation occurred, and the animals died in from eighteen to thirty hours, showing in every instance at autopsy marked con-

6. Snapper, J.: Ueber den Zusammenhang zwischen Funktion der Nieren und Chlorretention bei fieberhaften Krankheiten, *Deutsches Arch. f. klin. Med.* **111**: 430, 1913.

7. Dragstedt, C. A., and Mullenix, R. B.: Experimental Esophageal Fistula, *J. Lab. & Clin. Med.* **16**:591, 1931.

solidation of the lungs. In five dogs the obstruction was made by gradually tightening a metal clamp with rubber-covered jaws around the esophagus until it was occluded. In one of these dogs swallowing efforts were promptly made, and the animal died in twenty-eight hours, showing pneumonia at autopsy. The remaining four animals survived indefinitely, the clamp cutting through and establishing a fistula in three, four, four and six days, respectively, after which they were fed through the esophageal fistula. Until the establishment of the fistula, 500 cc. of 5 per cent dextrose was administered daily.

4. *Esophageal Obstruction After Preliminary Esophageal Fistula.*—From group 3 it was apparent that when the operative hazard incurred in obstructing the esophagus was eliminated by obstructing it some time after it had been exteriorized, there was still the hazard of 50 per cent or more animals developing an aspiration pneumonia, but in those animals that escaped the pneumonia there was no toxemia incident to the obstruction and they could survive until the obstruction relieved itself by the cutting through of the clamp. As we desired to produce a complete permanent obstruction, and as it seemed from the experiments in groups 2 and 3 that aspiration pneumonia would be precluded by preliminary esophageal fistula, we operated to obstruct the esophagus in a number of animals after first preparing a fistula of the esophagus in the neck. The fistula was prepared by the two-stage procedure described elsewhere,⁷ and consisted, in brief, of exteriorizing a portion of the esophagus in the neck and some time later incising the anterior wall of the exteriorized portion.

In six animals the obstruction was made intra-abdominally by sectioning the cardia of the stomach and inverting both ends, from five to ten days after the preparation of the fistula in the neck. A gold-plated cannula was inserted into the stomach at this operation for purposes of feeding. Five of the animals died in from two to seven days. In four of these, definite cause for death was found post mortem, hemorrhage and peritonitis giving evidence of technical failure of the operation. In one no evident cause for death was found post mortem, but we are not inclined to attribute the death to toxemia from the obstruction as it is well known that the trauma and shock associated with sectioning both vagi below the diaphragm and the necessary stretching of the cardia involved in the operation are of serious significance. One animal, in which the operative procedures were carried out more skilfully, survived and did well until the eighth day, when it contracted distemper, and died on the eleventh day.

As we thought that possibly the operative hazard might be lessened by obstructing the esophagus intrathoracically above the diaphragm, this was done in ten dogs. Pentobarbital sodium was used as the

anesthetic in these animals, and artificial respiration was maintained by positive pressure insufflation of air through a catheter in the trachea. The incision was made through the eighth interspace on the left side. In eight animals the esophagus was carefully freed in its lower portion, the branches of the vagi being separated as far as possible. The esophagus was then sectioned with a knife about 3 cm. above the diaphragm and both ends were inverted and sutured with silk. The dogs died in from three to seven days, showing at postmortem examination varying degrees of empyema and mediastinitis. As we were convinced that we could not prevent a certain amount of soiling with subsequent bacterial infection by using the knife to section the esophagus, in the remaining two dogs the esophagus was sectioned with the cautery. The first one of these survived and remained well until the tenth day, when a subcutaneous infection developed, apparently induced by a subcutaneous administration of 5 per cent dextrose, and the dog died on the thirteenth day. At autopsy there was no empyema, pneumonia or mediastinitis, and the sutured ends of the esophagus were firmly closed. The second dog survived, and, in spite of a mild distemper and subcutaneous infection, it has made a good recovery and is now alive and doing well one month after the operation. Beginning on the second postoperative day, water was administered through the gastric cannula; on the fourth day milk was added, and since the seventh day a ration of milk, bread, eggs and ground steak has been fed.

COMMENT

It was apparent early in the work that there is a considerable surgical hazard in operative procedures on the esophagus. In such a relatively simple procedure as making a fistula in the neck, there is a mortality due to infection of over 50 per cent if the operation is done at one stage. That clinical surgeons have appreciated this is borne out by numerous papers and is well expressed in the review of esophageal surgery by Saint.⁸ It was necessary, therefore, to separate and distinguish this hazard from the physiologic consequences of the obstruction. This can readily be done by first exteriorizing the esophagus in the neck, after which it can be obstructed without any surgical hazard whatever. When the obstruction was made by tying a stout ligature around the exteriorized portion, violent swallowing efforts immediately began, attended by profuse salivation, and the animals died within thirty-six hours, showing at postmortem examination an aspiration pneumonia with the lungs appearing the same as in a drowned person. When the obstruction was made with a rubber-jawed clamp, such swallowing efforts did not occur in four of the five instances, and the animals survived

8. Saint, J. H.: Surgery of the Esophagus, *Arch. Surg.* **19**:53 (July) 1929.

indefinitely and without any special treatment, the clamp cutting through by the third to the sixth day, thus establishing a fistula. With the latter procedure there was apparently not the same sensory stimulation provoking swallowing efforts as there was when the ligature was used.

These experiments demonstrated that in addition to the surgical hazard of operative procedures on the esophagus there was also a considerable likelihood of aspiration pneumonia. They also demonstrated that an obstruction could be produced and exist for from three to six days without producing any toxemia in the animals that escaped the pneumonia. This is also borne out by the experiments of Allen, published in 1925,⁹ who successfully temporarily obstructed the esophagus in both the neck and the chest by ligating beneath a circular patch of fascia lata so that, as the ligature cut through the esophagus, leakage was prevented by the fascial transplant. He did not mention whether or not any of his animals developed pneumonia.

The experiments in group 4 again emphasized the grave risk from infection experienced in operations in which the lumen of the esophagus is opened. The last two experiments, we believe, however, prove that a complete permanent obstruction can be produced if the surgical technic is satisfactory, without the development of toxemia or loss of gastrointestinal secretions, and that there is, therefore, no essential discrepancy between the physiologic mechanisms of the dog and of man.

CONCLUSIONS

There is no toxemia specifically related to esophageal obstruction in dogs, and dogs can survive indefinitely a permanent complete obstruction without special therapeutic measures.

Acute esophageal obstruction in dogs leads to the development of an aspiration pneumonia in a high percentage of cases. The operative procedures employed in producing acute esophageal obstruction are attended with an extreme surgical hazard from infection. These facts are to be appreciated and distinguished from the physiologic consequences of the obstruction itself.

9. Allen, D. S.: Further Experimental Reconstruction of the Esophagus with Autogenous Fascia Lata Transplants, *Arch. Surg.* **10**:374 (Jan.) 1925.

FORTY-SIXTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY *

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CONGENITAL DEFORMITIES

Cervical Rib.—Telford and Stopford¹ recorded three cases of cervical rib in which the prominent symptoms were due to thrombotic obliteration of the arteries of the arm. These cases resembled one another in their gradual onset, the initial pallor, coldness and numbness of the limb, the occurrence of gangrene and the cessation of all pulse at a point about the junction of the axillary and brachial arteries, and finally in their complete recovery following the removal of a cervical rib. In no case was the subclavian artery found at operation to be constricted. Telford and Stopford believed the thrombosis to be due to irritation of the sympathetic nerve fibers supplying the peripheral arteries. They demonstrated by histologic sections that these sympathetic nerve fibers lie in the lowest trunk of the brachial plexus, and are therefore liable to compression by a cervical rib. They assumed that the compression irritated the sympathetic fibers and the irritation

* This Report of Progress is based on a review of 200 articles selected from 399 titles dealing with orthopedic surgery appearing in the medical literature between April 11, 1931, and June 27, 1931, supplemented by a few selected articles of older date. Only those papers that seem to represent progress have been selected for review.

1. Telford, E. D., and Stopford, J. S. B.: Brit. J. Surg. **1**:557, 1931.

caused spasm of the walls of the arteries; this spasm embarrassed the vasovasorum, which led to deterioration in the arterial walls and consequent thrombosis. In support of this hypothesis they produced experimentally a similar thrombosis by injecting ergot into cockerels.

Congenital Dislocation of the Hip.—Lowman² reported a procedure which he called “the double leaf shelf operation.” A new acetabulum was made as low on the ilium as possible. Two rectangular bone flaps were then cut and turned down, one forward and downward, the other backward and downward. The adjacent corners of these flaps were sutured together with chromic catgut, and bone chips, obtained in large part from the removal of the upper margin of the original acetabulum, were packed back of the flaps. A check suture tied to the greater trochanter held the flaps in place.

[ED. NOTE.—The “shelf operation,” in this country at least, is well established. The choice of operation is not so important as the careful performance of whatever operation is chosen. Lowman’s operation offers another choice. We question the advisability of suturing the shelf to the trochanter.]

A Simple Modification of Putti’s Splint for the Early Treatment for Congenital Dislocation of the Hips.—Coonse³ combined traction with abduction in using Putti’s splint for congenital dislocation of the hip in children 1 to 4 or 5 years of age. Skin traction was used, and the traction ropes were carried over large wooden pulleys at the ends of the splint and fastened to a spring balance scale. Usually 5 or 6 pounds of traction were sufficient to accomplish reduction.

BACK PAIN AND SCIATIC PAIN

Studies of the Nucleus Pulposus.—Geist,⁴ basing his paper on the work of Schmorl, noted the frequent affection of the intervertebral disk and nucleus pulposus by disease and injury. The intervertebral disk comprised about one fourth of the movable parts of the spine, 40 per cent in the cervical region, 33.3 per cent in the lumbar and 20 per cent in the dorsal regions. Pathologic conditions of the spine in which the disk played a prominent part were: (1) prolapse of the disk, (2) adolescent kyphosis, (3) poor posture, (4) osteoporosis, (5) senile changes and (6) chronic spondylitis, which was always preceded by changes in the disk usually of the type of cartilage prolapse. In the following conditions the pathologic process of the disk was of secondary nature: 1. In fractures of the vertebrae the disk was often injured. 2. In injury without fracture there was frequently prolapse of the disk. 3. In sco-

2. Lowman, C. L.: J. Bone & Joint Surg. **13**:511, 1931.

3. Coonse, G. K.: J. Bone & Joint Surg. **13**:602, 1931.

4. Geist, E. S.: Intervertebral Disk, J. A. M. A. **96**:1676 (May 16) 1931.

liosis the rôle of the disk had not yet been determined, but it probably played a part. 4. In osteomalacia there were softening of the bone and consequent ballooning of the disk. 5. In tuberculosis of the spine the disk frequently disappeared early in the disease. 6. In osteomyelitis the disk was rapidly destroyed. 7. Syphilis of the spine was characterized by bony density and cartilage prolapse. 8. Charcot spine was characterized by marked hyperostoses and disappearance of the disk. 9. Carcinoma, or other destructive bone lesions, often showed cartilage prolapse into the substance of the bone.

Sashin⁵ discussed the significance of intervertebral disk extension into the adjacent vertebral bodies. He had studied the condition, roentgenologically and at autopsy, and felt that in the great majority of cases trauma, either acute or repeated over a long period of time as in the case of men employed at hard labor, was the etiologic factor. In some instances the lesion might be caused by degenerative changes of the cartilaginous plate of the vertebral body by the expansile disk, as seen in osteomalacia, tumor metastases and osteoporosis, when the resistance offered by the vertebra was lowered. The author gave full credit for the knowledge of intervertebral disk disease to Schmorl, who first described it in 1926.

Fibrocartilaginous Nodules of Intervertebral Disk Causing Compression of the Spinal Cord.—Alajouanine and Petit-Dutaillis⁶ made a study of the anatomy and pathogenesis of the new variety of radiculomedullary compression caused by fibrocartilaginous nodules of the posterior face of the intervertebral disk. They found a report of twenty-one cases in the literature of which in ten cases the location of the tumor was in the lumbar region, in three cases in the dorsal region and in seven cases in the cervical region. They reported two cases of their own, both with unilateral lumbosciatic pain of from three to four years' duration before motor disturbances appeared finally leading to the diagnosis. In both cases the tumor was situated in the lower lumbar region. They emphasized the fact that the nodules were almost invariably in a lateral rather than a median location.

Discussing the significance of these tumors, the authors stated that in view of the studies of Schmorl and Androe it seemed probable that the starting point of the lesion was a herniation of the nucleus pulposus through a fissure in the posterior part of the disk. To account for the herniation of the disk there were the traumatic theory and the theory of previous alterations of the nucleus and of the disk itself.

[ED. NOTE.—The editors agree that the intervertebral disk is coming into its own as a recognized factor in pathologic conditions of the spine.

5. Sashin, D.: Intervertebral Disk Extensions Into Vertebral Bodies and Spinal Canal, *Arch. Surg.* **22**:527 (April) 1931.

6. Alajouanine, T., and Petit-Dutaillis, D.: *Presse méd.* **38**:1657, 1930.

They wish to point out, however, that many variations of the disk probably occur that are without pathologic significance.]

A Groove for the Hypogastric Vessels.—Ferguson⁷ pointed out that in the roentgenologic diagnosis of arthritis of the sacro-iliac joints error might arise when a groove in the ilium for the hypogastric vessels caused the inferior margin of the joint on the iliac side to appear sharply pointed, simulating the osteophytic outgrowth or lipping of arthritis. The prevalence of this groove was not generally recognized. A recent examination of the films of a hundred patients showed the groove present in some degree in eighty-six.

RICKETS AND CALCIUM METABOLISM

In a recent study of the replacement of the bone salts in healing scurvy, Salter and Aub⁸ tried to determine whether or not the stores of lime salts in the bone were depleted at the same time that calcification of the growing portion was inhibited by lack of the antiscorbutic vitamin. At various stages of the disease in experimental animals the missing vitamin C was supplied in the form of orange juice and at the same time alizarin was injected so that the newly deposited bone salts would be stained red, and thus be easily detected. It was found that in healing scurvy the epiphyseal line was especially well marked, indicating a deposition of salts in the zone of rapid calcification. Furthermore, the cancellous tissue of the epiphysis and diaphysis was also stained, the pink trabeculae extending a short way into the medullary cavity. In addition, the shaft was colored by the dye distal to the epiphysis, although not as deeply red as were the trabeculae. On the other hand, the bones of animals receiving no source of vitamin C whatever remained unstained by the dye in spite of the fact that the experimental ration contained calcium and phosphorus.

In other words, scurvy was a derangement of calcification of the bones which affected the storage of bone salts in the trabecular tissue as well as the deposition in the epiphyseal region.

Fibrous Osteodystrophy in Experimental Hyperparathyroidism in Guinea-Pigs.—Jaffe and his co-workers⁹ studied the effect of single and repeated doses of parathyroid extract in guinea-pigs. After a large single injection (20 units per hundred grams of weight) into young guinea-pigs, definite histologic changes were observed in six hours. Forty-

7. Ferguson, A. B.: J. Bone & Joint Surg. **13**:568, 1931.

8. Salter, W. T., and Aub, J. C.: Studies in Calcium and Phosphorus Metabolism: Deposition of Calcium in Bone in Healing Scorbutus, Arch. Path. **11**:380 (March) 1931.

9. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Fibrous Osteodystrophy (Osteitis Fibrosa) in Experimental Hyperparathyroidism of Guinea-Pigs, Arch. Path. **11**:207 (Feb.) 1931.

eight hours after injection the decalcification was so intense that the cortices of the ribs were fractured. Hemorrhage was observed in the marrow cavity; there were dilatation of the blood vessels and slight fibrosis of the marrow. There was cessation of all bone formation. The serum calcium tended to be higher from twenty-four to forty-eight hours after injection. The serum phosphorus remained within normal limits. When the guinea-pigs had fasted twenty-four or more hours before the injection there was a more definite rise in the serum calcium and also a rise in the phosphorus. In adult guinea-pigs there was no definite histologic change in the bones after single injections of parathyroid extract, although a rise in the serum calcium and phosphorus was observed. Repeated small doses of parathyroid extract in young pigs produced extensive fibrosis of the marrow and enlargement of the blood vessels, but no extensive formation of osteoid tissue. Larger doses had a more definite effect. Destructive lesions were seen in the bone marrow cavity with osteoid tissue formation in the healing process. Where the destructive lesion produced a sufficiently severe disturbance in the circulation, cyst formation resulted.

Ingestion of food was found to be an important factor in modifying the effect of the injection of parathyroid extract on the serum calcium and phosphorus. With small repeated doses, no definite rise in the calcium and phosphorus was observed. With large doses, the calcium was markedly elevated. The authors concluded that the changes produced in guinea-pigs were of the same order as those described for osteitis fibrosa without osteoid tissue in man.

NEOPLASMS

Metastatic Lesions of the Bones.—The analysis by Copeland¹⁰ of 334 cases of metastatic lesions of the bone was one of the most comprehensive available. In the 1914 series of primary breast tumors there were 100 cases with bone metastasis. The bones most frequently involved were in order of frequency, the spine, pelvis, femur, skull, ribs and humerus. These lesions were most often multiple, being single in only one fourth of the cases. The most common type of lesion was an osteolytic lesion, while a sclerosing lesion was encountered only twice in the series. Roentgen therapy gave relief from the excruciating pain, and in some instances definitely prolonged life. Of 1,040 cases of primary prostatic carcinoma, there were 134 with bony metastases. Only 50 per cent of the patients, however, were examined by the roentgen rays, and in only 25 per cent of this number were metastases found. The bones most frequently involved were the pelvis and vertebrae, and the metastatic lesions were all predominantly osteoplastic. Of 63 cases of hypernephroma, 22 showed bony metastases. The bones

10. Copeland, M. M.: Radiology **16**:198, 1931.

affected were in order of frequency, humerus, spine, femur, pelvis, ribs, bones of the feet, skull and sternum. It was to be noted that this was the highest incidence of bone involvement found in the entire series, there being bony metastases in 34.9 per cent of the cases, while in prostatic carcinoma it amounted to 12.8 per cent, in breast tumors to 5.2 per cent and in lung carcinoma to 16.6 per cent (four cases).

Neoplastic Lesions of the Upper End of the Humerus.—Major,¹¹ reviewing the neoplastic lesions of the upper end of the humerus, noted the following points:

1. The two most frequent osteolytic lesions did not require surgical intervention. They were the benign cyst and the malignant metastatic tumor the origin of which was elsewhere than the defect in the bone. The bone cyst was best left alone, or, if a pathologic fracture had occurred, treated by light roentgen radiation. The metastatic tumor was best treated in this late stage by heavy doses of deep roentgen radiation.

2. In all other cases in which the nature of the tumor was doubtful, the wise procedure seemed to be to put the arm at rest, administer roentgen therapy and obtain competent consultation on the roentgen films, rather than to do an immediate exploration for microscopic examination.

3. Resection in all malignant lesions of the upper end of the humerus offered as much for cure as did amputation and more for the patient, if cured.

Neoplastic Lesions of the Lower End of the Radius.—Oliver¹² studied fifty lesions of the lower end of the radius. Of the various neoplasms encountered in the radius, 90 per cent were in the lower end, and of these, thirty-five, or 70 per cent, were giant cell tumors. Other conditions were exostoses, 8 per cent; nonsuppurative osteomyelitis, 6 per cent, and bone cyst, 6 per cent. One case each, or 2 per cent, was noted of chondroma, chondrosarcoma, Ewing's tumor, osteolytic sarcoma and sclerosing sarcoma. All the patients with benign lesions had been cured, and of the patients with giant cell tumors 74 per cent had required only one treatment by curettement and thermal or chemical cauterization.

Tumors of the Os Calcis.—Of 1,740 tumors reviewed at the Johns Hopkins Surgical Pathological Department, Moore¹³ found that 33, or 2 per cent, involved the os calcis. Exostosis was the most common type of new growth, occurring in 23 of the total number. All were treated by excision; cure was obtained in 20, and in 3 there was

11. Major, R. C.: Radiology **16**:224, 1931.

12. Oliver, R. L.: Radiology **16**:245, 1931.

13. Moore, J. R.: Radiology **16**:232, 1931.

recurrence. No malignant changes were observed in this series. Chondroma, giant cell tumor, chondrosarcoma and Ewing's tumor composed the remainder. No bone cysts, myeloma or metastatic tumors were found. Chondromas of the os calcis had to be treated in the same manner as chondromas of the long bones. They ought to be watched carefully with frequent roentgen examinations and the malignant possibilities borne in mind. If malignant changes became evident, they were to be treated as chondrosarcomas, and early amputation offered the only hope. The giant cell tumors, when recognized before the shell perforated, responded to curettage, and apparently had little tendency to recur. Excision or amputation might be necessary when the invasion of the soft part was extensive. Ewing's tumor offered little hope for life, judging by the two cases reported. However, in neither case was the diagnosis made before the end of twenty-four months. It is possible that with early diagnosis, amputation and roentgen therapy might have helped.

Nonsuppurative Osteomyelitis.—Cohn¹⁴ studied 105 cases of non-suppurative benign lesions of bone grouped under the diagnosis of Paget's disease, ossifying periostitis and nonsuppurating osteomyelitis. More than one bone was involved in 25 per cent of the cases; the remaining 75 per cent showed single lesions. The tibia and femur were each involved in about 20 per cent, the humerus in about 8 per cent, the skull in 5 per cent and the clavicle in 5 per cent. The remaining 35 per cent included lesions of the radius, ulna, fibula, metatarsal, metacarpal, carpal and tarsal bones, phalanges, ribs, vertebrae and jaw. In about 33 per cent the roentgen examination alone suggested that there was a question of sarcoma. There were four types of lesions: sclerosing, ossifying, destructive and osteoporotic, and four etiologic factors, viz., traumatic, syphilitic, posttyphoid, or postinfluenza and focal infections.

In respect to treatment, Cohn stated that "when the roentgen examination suggested sarcoma, and the tumor was radioresistant, and all foci of infection had been eliminated, exploratory operation was justified provided the tumor, if malignant, was operable."

Pathologic Lesions of the Bones of the Hands and Feet.—Kahn¹⁵ studied 140 pathologic lesions of the small bones of the hands and feet. Of forty cases of exostoses, the os calcis was involved in 50 per cent. The youngest patient was 7 years of age and the oldest 65. The chondromas numbered forty-five, and were almost equally divided as to sex. The youngest patient was 6 years of age, and the oldest 80. In thirty cases the phalanges of the hands were involved; in seven the

14. Cohn, L. C.: *Radiology* **16**:187, 1931.

15. Kahn, M.: *Radiology* **16**:211, 1931.

metatarsals; in six the phalanges of the feet, and in two the tarsals. There were no cases of chondroma involving either the carpals or the metacarpals, an important diagnostic point in differentiating this lesion from benign giant cell tumor and bone cyst. This study emphasized the rarity of malignant disease in the small bones of the hands and the feet. If a lesion was single in character and central and osteolytic in type, a malignant condition could be practically ruled out. Periosteal, osteogenic sarcoma occurring as a single lesion in the small bones of the extremities was rare. It had been found in about 2 per cent of the cases, and was difficult to differentiate from the more frequent lesion of ossifying periostitis. The usual tumor encountered in the bones of the hands and feet contained cartilage, and was either an exostosis or a chondromyxoma, both of which could be safely treated as benign. Most of the remaining tumors belonged to the giant cell group, or to the closely related group of osteitis fibrosa or xanthoma, which also were typically benign. When metastatic nodules occurred in the small bones, their nature could be readily discerned by the presence of diffuse involvement of the remainder of the skeleton, which was always associated with their presence in the small bones.

[Ed. NOTE.—The foregoing articles are a part of a group dedicated to Dr. J. C. Bloodgood by his pupils. They represent observations on material collected over many years, studied extensively, and followed up as accurately as possible. We therefore believe them to be of the utmost importance in leading toward a better knowledge of this most important subject, tumors of bone.]

Liposarcoma.—Stewart¹⁶ reported what he believed to be three cases of primary liposarcoma of the bone. All occurred in young men. In each case there were multiple bony tumors loaded with fat cells, and there was no evidence of their having originated from endothelium. The author felt justified in reporting these tumors as liposarcomas in the hope of encouraging other pathologists to look for similar tumors.

Benign Giant Cell Tumor.—Dyke,¹⁷ a pathologist, reported a case of benign giant cell tumor with a fatal termination after a clinical course of five years. The original lesion was in the patella; this was curetted. A local recurrence developed after three years, and the leg was amputated. Death took place one year later. At the autopsy metastases exhibiting the same structure as the primary tumor were demonstrated in the scalp, lung, kidneys and mediastinal and peritoneal lymph nodes. Photomicrographs of the primary and of the secondary tumors were given.

Orr had reported a second case. The leg was amputated in January, 1898, and death took place seven months later. Photomicrographs of

16. Stewart, F. W.: *Am. J. Surg.* 7:87, 1931.

17. Dyke, S. C., and Orr, J. W.: *J. Path. & Bact.* 34:259, 1931.

the primary tumor were unavailable, but those of the metastatic deposits in the lungs showed the typical picture of benign giant cell tumor.

POLIOMYELITIS

Experimental.—Harmon and his co-workers¹⁸ described the pre-paralytic symptomatology in monkeys after intracerebral inoculation with the virus of poliomyelitis. In from five to eight days after inoculation the animal became passive or restless. This was followed by a period of excitement with cries and tremors in the muscles. With this there was a rise in temperature of from 1 to 3 degrees. Spinal fluid changes were found not earlier than forty-eight hours before paralysis. There was increased pressure, and globulin was found. There was very little change in the white blood count. The erythrocyte sedimentation rate was increased about twenty-four hours after the onset of the paralysis.

Missed Infections, Abortive and Relapsing Cases of Experimental Poliomyelitis.—Harmon and his co-workers¹⁹ found that of 350 monkeys inoculated intracerebrally with the virus of poliomyelitis, 7 resisted infection and showed no symptoms, elevation of temperature or spinal fluid changes. Four of these animals later succumbed to a second inoculation. Other animals of the same incubation period, with preparalytic symptoms, rise in temperature, cerebrospinal fluid changes, but not paralysis, were classified as having abortive cases of experimental poliomyelitis. There were ten such cases. In nine reinoculation was done, and in five typical paralysis developed. The authors felt that such cases were better explained on the basis of a difference in susceptibility rather than as due to mild infection from an attenuated virus.

Dry Storage of Convalescents' Serum.—Lichtenstein²⁰ reported that at the Stockholm Epidemic Hospital, Sweden, the greater part of the store of serum for both prophylaxis and treatment had been kept in a dried form. The experience there showed that serum so stored retained its efficiency for a long time, two or three years at least.

TUBERCULOSIS

Tuberculous Spondylitis.—Doub and Badgley²¹ recognized three types of tuberculous lesions of the spine, depending, they believed, on what particular part of the blood supply of the vertebrae was involved. The three types were, first, central involvement of the vertebral body;

18. Harmon, P. H.; Shaughnessy, H. J., and Gordon, F. B.: J. Prev. Med. 5:115, 1931.

19. Harmon, P. H.; Shaughnessy, H. J., and Gordon, F. B.: J. Prev. Med. 5:139, 1931.

20. Lichtenstein, A.: Dry Storage of Convalescents' Serum, J. A. M. A. 96: 2102 (June 20) 1931.

21. Doub, H. P., and Badgley, C. E.: Am. J. Roentgenol. 25:299, 1931.

second, primary involvement of the anterior portion of the vertebrae, and third, a type which they chose to call intervertebral articular tuberculosis.

They were particularly interested by this last type, and reported three such cases. They were difficult to diagnose clinically, because of the usual absence of physical findings, and the roentgenogram furnished the only evidence. An abscess might, however, be present before roentgen changes had occurred. There was usually definite narrowing of the intervertebral space, but the contour of the adjacent bodies might be preserved, and only later could erosion of the adjacent bodies be demonstrated.

Calcification of Tubercles by Means of Viosterol in Experimental Chronic Tuberculosis.—Spies²² produced a chronic tuberculous infection in rabbits, and then gave large doses, from 2 to 5 cc., of viosterol every two to five days until the animals died. He observed a precipitation of calcium in the tubercles far greater in frequency and degree than in a series of control animals. The calcium deposit was almost entirely limited to the necrotic and caseous portion of the tubercle. The author suggested that smaller, nontoxic doses might be of value in the healing of tuberculous lesions.

Laminectomy in the Treatment for Pott's Paraplegia.—Basing their arguments on a personal experience with fifteen patients, Le Fort and Baudelot²³ defended the effectiveness of laminectomy in relieving paraplegia resulting from Pott's disease. In their fifteen patients there were no postoperative deaths, but three died from fifteen months to four years after the intervention. The results were described as excellent (normal gait) in two; good (walking possible) in two; moderate (improvement) in five; nil in two, and one case was too recent to classify. In four of the patients the paralysis was of the precocious type; in six of the delayed type. The operation had been performed in from four months to seven years after the onset. The authors emphasized particularly the frequency of bony compression of the spinal cord, this having been found in ten of eleven cases. In four of the cases no trace of external pachymeningitis had been found.

The authors had never found any evidence of compression from an abscess. Their operative results were also contrary to the traditional views; their four successful results had been observed in cases of delayed and progressive paralysis, usually considered incurable, while their failures had resulted entirely in the rapid and precocious type of paralysis.

The authors felt, however, that it was still very difficult to formulate the indications for operation. They thought that the high frequency

22. Spies, T. D.: *Am. Rev. Tuberc.* **28**:169, 1931.

23. Le Fort, R., and Baudelot: *Scalpel*, Liège, Jan. 10, 1931.

of bony compressions was an argument in favor of operation. They had decided to intervene in cases of sudden or rapidly developing paralysis if no improvement had been obtained at the end of one year, and in the delayed and progressive types at the end of six months. They concluded that the operation was relatively benign, and that its effectiveness had been demonstrated sufficiently to make it worthy of consideration more frequently than at present.

[ED. NOTE.—Le Fort and Baudelot's observations are of considerable interest, especially because they are in contradiction to the commonly held views. The high frequency of bony compression found naturally raises a question of the effectiveness of the preoperative treatment their patients had received, as we feel that bony compression can usually be prevented or relieved by measures directed toward obtaining hyperextension and thorough fixation of the spine. A finding in some of the editors' cases has been a tuberculoma, and this was not found in any of the cases reported by the foregoing authors. Their views will require confirmation before we can accept them completely.]

PYOGENIC INFECTIONS OF BONES

Maggot Treatment.—Baer²⁴ described the use of maggots, the larvae of the blow fly, in the treatment of eighty-nine patients with osteomyelitis. The maggots were grown under aseptic precautions, and were placed on the wound from twenty-four to forty-eight hours after operation had been performed. No dressing was required, but the wound was covered by a snug fitting wire screen cut to the size of the wound to prevent the maggots from crawling out. The maggots removed the dead tissue and much of the secretion from the wound. The reaction of the wounds became alkaline soon after the introduction of the maggots. The wounds were washed out every five days and new maggots introduced. Granulation tissue filled in rapidly, and the wounds usually were soon solidly healed. There had been a recurrence of the osteomyelitis in 5 per cent of the cases. Such recurrences generally consisted in the extrusion of small spicules of bone after which the wounds remained healed. In a small number of cases with open tuberculous abscesses, encouraging results were obtained by wide incision of the abscess followed by maggot treatment. The author felt that in addition to the scavenger action, the maggots exerted some biochemical effect on the wound which was inimical to bacterial growth and hastened tissue repair.

[ED. NOTE.—No form of treatment has created more widespread discussion in the last few years than Dr. Baer's maggot treatment for

24. Baer, W. S.: J. Bone & Joint Surg. **13**:438, 1931.

osteomyelitis. We hope that the untimely death of its author will not interfere with the continuation of experiments aiming to evaluate it properly. We are of the opinion, however, that technical difficulties will prevent any general adoption of it.]

An Evaluation of the Orr's Treatment for Osteomyelitis.—Kulowski²⁵ made a study of 130 cases of osteomyelitis, 16 case of suppurative arthritis and 9 of extensive soft tissue suppuration, with treatment by Orr's method, and drew highly eulogistic conclusions. He recommended the method for routine use, claiming that it was painless, that it reduced the period of hospitalization, that it insured good functional results, and that it brought about improvement in the general condition of the patient, minimized loss of limb, shortened the postoperative course and was suited to the rank and file of the profession. It was attended by an insignificant mortality rate.

[ED. NOTE.—The article by Kulowski is thorough, and presents all of the arguments in favor of Orr's treatment. We believe that in the treatment for osteomyelitis thorough operation and adequate drainage are more important than the particular type of postoperative treatment employed.]

Epithelization of Bone Cavities and Calcification of Fibrous Marrow in Chronic Pyogenic Osteomyelitis.—Brunschwig^{25a} reported a histopathologic study of three cases of chronic pyogenic osteomyelitis of over fifty years' duration, which showed:

1. Epithelization of the draining sinuses and partial to nearly complete epithelization of large cavities in the bone to which they led.
2. Calcification of fibrous marrow in cancellous bone bordering the cavities with infection and necrosis and partial or complete sequestration of these bony and calcified areas.
3. Calcification in fibrous marrow away from the epithelized cavities, surrounded and traversed by living bone.

As to treatment, two of the three patients died after amputation which had seemed advisable because of the inconvenience and pain caused by the lesion over a period of many years. In the third patient, in whom more conservative treatment was employed, the cavity being extensively effaced by removal of much of its walls and all sequestrums, foreign bodies and soft parts, no relief from pain or purulent discharge was obtained. The condition of the leg remained essentially the same as before operation. In fact, the cavity had become relined

25. Kulowski, J.: J. Bone & Joint Surg. **13**:538, 1931.

25a. Brunschwig, A.: Surg. Gynec. & Obst. **52**:759, 1931.

with epithelium at the end of two years, and there appeared to be no reduction in the amount of discharge.

[ED. NOTE.—The authors' studies confirm our opinion that extensive osteomyelitis of many years' duration does not lend itself to an operation for radical cure.]

(To be Concluded)

THE BACTERIOLOGY OF ABSCESS OF THE LUNG AND METHODS FOR ITS STUDY *

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There is a great deal of disagreement in the literature as to the presence or absence of anaerobes in the fetid pus of suppurations from the lung. In 1893, Veillon examined the bacteriology of fetid pus and first pointed out the rôle of anaerobes in these cases. In 1898, Veillon and Zuber¹ studied systematically the diseases characterized by gangrene; they isolated a number of anaerobic organisms and concluded that this process is elicited by them. This was confirmed by Hallé,² Rist³ and Cottet.⁴ Guillemot⁵ later applied the technic of Veillon and Zuber in the study of pus from pulmonary suppurations. He found *Bacillus ramosus* in eight of thirteen cases, *B. fragilis* in six, *Micrococcus foetidus* in three, *B. thetoides* in three, *B. fusiformis* in two and *Staphylococcus parvulus* in one. He ascribed to *B. ramosus* an important rôle in the pathogenicity of abscess of the lung when it is associated with another organism, such as the streptococcus.

Since 1898, a great deal of discussion has arisen in the literature as to whether anaerobes are actually found in suppurations of the lung. In fact, their presence in cases of abscess of the lung was entirely ignored in the later literature on the subject, probably because of the difficulty of their isolation. While it is true that fusiform bacilli and spirochetes were isolated by Smith⁶ and noted by other observers on

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* From the Laboratories of Mount Sinai Hospital and from the Surgical Service of Dr. Harold Neuhof.

1. Veillon and Zuber: Recherches sur quelques microbes strictement anaérobies et leur rôle en pathologie, Arch. de méd. expér. d'anat. path., July, 1898.

2. Hallé: Recherches sur la bactériologie du canal génital de la femme, Thèse de Paris, 1898.

3. Rist: Anaerob pathogens et suppurative gangreneuse, Bull. Inst. Pasteur 3:49, 1905.

4. Cottet: Recherches bactériologique sur les suppuration péri-urétrales, Thèse de Paris, 1899.

5. Guillemot: Recherches sur la gangrène pulmonaire, Thèses de la Faculté de Médecine, 1898.

6. Smith, D. T.: Fuso-Spirochaetal Disease of the Lungs, Am. Rev. Tuberc. 16:584, 1927.

direct spreads of pus (Kline,⁷ Pilot and Davis,⁸ Arnheim,⁹ Bezançon,¹⁰ Farah,¹¹ Castellani,¹² Nolf,¹³ Seguin and Kritchewsky,¹⁴ Fishberg and Kline,¹⁵ Buday¹⁶ and Bykowa¹⁷), the organisms described by Guillemot⁵ (i. e., *B. ramosus*, *B. fragilis*, *M. foetidus*, *B. thetoidis*, *B. fusiformis* and *Staph. parvulus*) were not found or were lost sight of entirely. Hartwell¹⁸ found *Staphylococcus aureus* the predominating organism in abscess of the lung as recently as 1920. He concluded that *Staphylococcus aureus* was an important agent in the formation of abscesses. Lyman¹⁹ believed that no special organism can be held accountable. In 1924, Lambert and Miller,²⁰ studying the bacteriology of abscess of the lung, found various anaerobes which they designated as gram-positive bacilli, gram-negative bacilli, cocci and streptothrix. They did not report cultures, nor did they attempt a systematic bacteriologic study. They concluded that the striking feature of abscess of the lung was that only anaerobes were found. On the other hand, Ermatinger²¹ insisted that hemolytic *Staphylococcus aureus* is the pyogenic organism most frequently encountered. He found it in 80.75 per cent of cases. The hemolytic streptococcus was found in the others. Bucher,²² also, concluded that the streptococcus was the organism found in 79 per cent of cases studied. Of the organisms found, those next in importance were *Staphylococcus aureus* and *albus*. More recently,

7. Kline, B. S.: Experimental Gangrene, *J. Infect. Dis.* **32**:481, 1923.

8. Pilot, I., and Davis, D. J.: Studies in Fusiform Bacilli and Spirochetes, *Arch. Int. Med.* **34**:313 (Sept.) 1924.

9. Arnheim: Die Spirochäten bei Lungengangrän und ulzerierenden Carcinom (Kultur-Versuche), *Centralbl. f. Bakt.* **59**:20, 1911.

10. Bezançon, F., and Etchegoir, E.: Spirochaeta bronchialis et gangrène pulmonaire, *Compt. rend. Soc. de biol.* **94**:319, 1926.

11. Farah: Spirochetose bronchique, *Presse méd.* **27**:774, 1919.

12. Castellani: Bronchial Spirochetosis, *Brit. M. J.* **2**:782, 1909.

13. Nolf, P.: Fetid Spirillar Bronchitis and Pulmonary Gangrene, *Arch. Int. Med.* **25**:429 (April) 1920.

14. Seguin and Kritchewsky: Spirochetose buccales, *Rev. de stomatol.*, 1920-1922, p. 613.

15. Fishberg, M., and Kline, B. S.: Spirochetal Pulmonary Gangrene, *Arch. Int. Med.* **27**:61 (Jan.) 1921.

16. Buday: Histologische Untersuchungen über die Entstehungsweise der Lungengangrän, *Beitr. z. path. Anat. u. z. allg. Path.* **48**:70, 1910.

17. Bykowa, O.: Zur Ätiologie der Lungengangrän, *Virchows Arch. f. path. Anat.* **258**:617, 1925.

18. Hartwell, J. A.: Abscess of the Lung, *Ann. Surg.* **72**:333, 1920.

19. Lyman, H. W.: Abscess of the Lung, *South. M. J.* **15**:744, 1922.

20. Lambert, A. V. S., and Miller, J. A.: Abscess of the Lung, *Arch. Surg.* **8**:446 (Jan.) 1924.

21. Ermatinger, L. H.: Microorganisms of Lung Abscess and Bronchiectasis, *J. Infect. Dis.* **43**:390, 1928.

22. Bucher, C. J.: Abscess of the Lung, *Am. J. M. Sc.* **174**:406, 1930.

Varney²³ described an anaerobic organism, *B. melaninogenicum*, in abscess of the lung. He believed that this organism played a significant rôle in its production.

As is seen, some observers ascribe prominence to *B. fusiformis* and to spirochetes, others to pyogenic organisms alone, while Varney attached an important rôle to *B. melaninogenicum*. In view of the confusion in the literature on the subject, the importance of a thorough study of the bacteriology of this disease entity is evident. While anaerobes are noted in certain instances, their isolation either is not attempted or is impossible because of lack of proper technic and apparatus. While the pus taken at operation may show various cocci, gram-positive and gram-negative bacilli, fusiform bacilli and spirochetes, even after twenty-four hours few of these organisms are found in cultures. Some observers, notably Varney and Smith, though able to isolate certain of these organisms, fail to isolate others.

The work reported in this paper was done in order to study culturally the entire bacterial flora of abscess of the lung. In a problem of this scope, it was thought desirable and important first to attack it from the point of view of the methods already available, and if these were found wanting to devise a simple and practicable procedure for the cultivation of the anaerobic flora in suppurations of the lung. To define the premise on which the conception of a strict anaerobe should rest was the next task.

STUDIES ON CONDITIONS FOR ANAEROBIC GROWTH

Media.—The Smith-Noguchi Medium: This medium was prepared from ascitic fluid to which 1 per cent of dextrose and 1 per cent of peptone broth were added. Ten cubic centimeters of this fluid was poured into a long, narrow test tube, 20 by 1.5 cm., which contained a piece of fresh sterile rabbit's kidney. This was incubated overnight for sterility.

Blood Plates: To 5 cc. of citrated blood was added 95 cc. of plain agar with a p_H of 7.4, melted in the Arnold steam sterilizer and cooled to 45 C.; the mixture was then poured into plates.

Ascitic Fluid Agar: Sixty-five cubic centimeters of ascitic fluid with a p_H of 7, was added to 150 cc. of 2 per cent dextrose agar, with a p_H of 7.8, at 50 C., and plates were poured from this mixture.

Sugar Media: The sugar media used were prepared in accordance with the directions given by Murray.²⁴

23. Varney, P. L.: Bacterial Flora of Treated and Untreated Abscesses of the Lung, Arch. Surg. **19**:1609 (Dec.) 1929.

24. Murray: Sugar Media for Meningococci, Medical Research Council, publication no. 124, London, His Majesty's Stationery Office, 1929.

Gelatin and Litmus Milk: In order to make it possible for strict anaerobes to grow in gelatin or in litmus milk, a piece of rabbit's kidney was added.

All fluid mediums were covered with petrolatum seal before incubation.

Methods of Anaerobiosis.—Method of Surface Culture: In pus containing from four to ten different organisms, the most feasible method of isolation is by the surface growth of individual colonies. This offers an opportunity for the study of their cultural characteristics and their morphology.

Various factors that were likely to influence the growth of anaerobic organisms on the surface of plates were studied as follows:

(a) Time of exposure to air: The time elapsing between the moment of inoculating the plates, the final disposition in the jar and the production of anaerobiosis is undoubtedly of great importance. At best, from thirty minutes to an hour can be counted as the minimum, at which time the exposure to aerobic conditions injures the anaerobic organisms. Barber²⁵ pointed out that some strict anaerobes may be destroyed even by exposure of less than an hour to atmospheric oxygen.

(b) Moisture inside the anaerobic jar: The growth of delicate anaerobic organisms on the surface of plates requires more moisture than does the growth of aerobic organisms. One method of supplying moisture to the plates is by making the jar moist.

(c) Effect of pus on the growth of anaerobes: Studies on the conditions of anaerobic cultivation of the anaerobic flora of abscess of the lung suggested the fact that the pus in which the organisms originated promotes their growth on the surface. That this factor is efficacious in influencing their growth also under aerobic conditions is shown in the following statement: When thick sticky pus containing anaerobic organisms is spread on a blood plate and incubated aerobically, the part of the plate where the pus is thickest will show the survival of some of the anaerobic organisms.

In this connection it is interesting to note that Shearer²⁶ observed the favorable effect of the accessory factors of growth contained in the nasal secretion and in the spinal fluid on the growth of meningococci.

For these reasons a routine procedure was adopted of centrifugating every twelve to twenty-four hour fresh culture in Smith-Noguchi medium; the supernatant fluid was discarded, and the pussy sediment was used for inoculating the plates.

25. Barber, M. A.: Use of Single Cell Method in Obtaining Pure Cultures of Anaerobes, *J. Exper. Med.* **32**:295, 1920.

26. Shearer, G.: On the Presence of Accessory Food Factors in the Nasal Secretions, *Lancet* **1**:59, 1917; On the Action of Spinal Fluid, *ibid.* **2**:714, 1917.

(d) Effect of gum arabic: A growth-promoting effect was also observed when gum arabic instead of pus was used on the surface of the plates. The following method was employed:

One cubic centimeter of sterile 10 per cent solution of gum arabic in peptone broth with a p_n 7.4 is spread over a blood plate. One drop of a twenty-four hour culture of a strict anaerobe—*Staph. putridus* (obtained through the courtesy of Dr. Schottmüller)—is mixed with the gum arabic-bouillon solution. This plate is incubated aerobically. A drop of the same twenty-four culture is spread on another blood plate, and is also incubated aerobically. Within from twenty-four to forty-eight hours, the blood plate containing the gum arabic will show a scant growth of the strictly anaerobic organism. The second blood plate, inoculated with the culture alone, will not show a growth.

(e) Influence of pressure exerted on the plate by the inoculating needle: Finally, the most important factor responsible for the growth of anaerobic organisms on the surface of plates is the pressure with which the inoculating needle submerges the organism just under the surface of the agar. Thus, if a drop of pus is spread on the surface of a blood plate with an ordinary platinum wire, no growth of the strict anaerobes will result. If, on the other hand, a heavy platinum wire is used and firm pressure is applied, growth of individual colonies will result. Varney,²⁷ using the principle of pressure, devised a revolving stand with a stationary inoculating needle. He called it the spiral streak plate method. The plate to be inoculated is placed on the stand and is revolved about the needle in a spiral fashion until the whole surface of the plate is covered. The reasons for the beneficial effect of pressure on the growth of anaerobes on the surface may be due to various factors: (1) by the additional pressure, the bacteria adhere better to the surface; (2) the high viscosity of pus requires greater pressure for the separation of the bacteria and (3) the tiny burrows or grooves in the agar mediums give the organisms additional anaerobic protection.

The Inoculating Brush.—A brush was designed in this laboratory which embodies the advantages of pressure and also, by the use of a number of inoculating points instead of the one ordinarily used, increases the opportunities for the isolation of rare organisms. Moreover, it has additional advantages in that it is economical to make in the laboratory and is convenient and easy to handle; the whole plate can be covered completely in much less time than it ordinarily takes to inoculate with a single platinum wire.

The brush consists of from fifteen to twenty strands of aluminum wire no. 8, about from 12 to 15 cm. in length. These strands are bound together and bent into the shape of a brush (fig. 1). Another strand

27. Varney, P. L.: A New Spiral Streak Plate Method of Isolating Bacteria by Means of Inoculating Machine. *J. Infect. Dis.* **41**:190, 1927.

of wire is wound around the handle. A brass clip (fig. 1 *b*) is fastened near the neck (fig. 1 *a*), which keeps the teeth of the brush separated. A number of such brushes can be made in a short time. They are boiled in soap and water, rinsed thoroughly in running water, dried and then sterilized in a metal container by dry heat for one hour. When ready for use, each brush is lifted out of the container with a pair of sterile forceps.

In inoculating plates, a drop of pus is placed at the periphery; the teeth of the brush are then thoroughly mixed with it, and parallel streaks are made. Cross-streaks perpendicular to these are also made. The plate finally appears like a ground work mosaic (fig. 2). Motion with the brush should be firm and steady, care being taken not to force the wire through the agar. The colonies of the different organisms will appear at the side of the streak, or will overgrow the grooved depressions. Thus they can be picked up under the microscope and seeded into fresh Smith-Noguchi mediums or into shake agar tubes.

Method of Shake Culture.—Another method for the isolation of single colonies is by shake culture prepared in the usual manner. The



Fig. 1.—Brush, consisting of from fifteen to twenty strands of aluminum wire, from 12 to 15 cm. in length. The brass clip (*b*) near the neck (*a*) keeps the teeth of the brush separated.

method has obvious disadvantages. The application of heat over the surface and the undue manipulation of the agar in separating it from the test tube cause it to become fragmented and turbid, which make the outlining of the colonies difficult. Another factor is the question of economy, for the test tubes are necessarily broken in separating the agar.

A simpler method for shake culture that I devised overcomes these difficulties. A glass tube open at both ends, of somewhat smaller diameter than the test tube to be used, is made to fit it not too snugly (fig. 3). The test tubes so prepared are sterilized by dry heat and filled with sterile melted agar in the ordinary manner. The agar of the inner tube is seeded at the proper temperature and then incubated. When ready for examination, the tip of a sterile forceps is inserted, and the inner tube is grasped, rotated a few times and removed. The test tube with the cylinder of agar is inverted over a sterile petri dish and is tapped so that the agar mold will fall out. Occasionally the inner tube will contain the agar mold when removed from the test tube. It can then

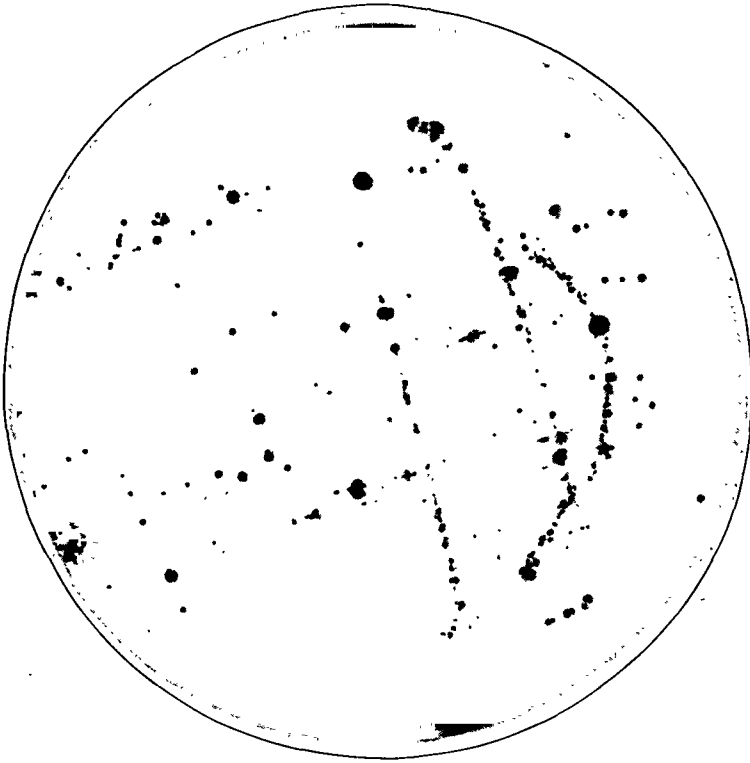


Fig. 2.—The mosaic appearance of the plate.

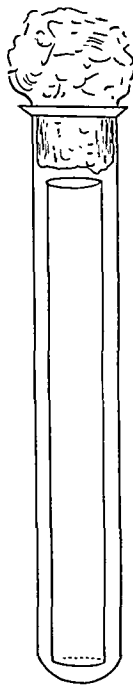


Fig. 3.—The simplified apparatus for shake culture devised by Cohen.

be put over a sterile petri dish, and with a sterile pipet the agar mold can be pushed out into the dish. The individual colonies are finally cut up and transferred to the proper mediums for further study.

The strictly anaerobic organisms failed to grow in solid mediums such as the shake agar tubes. The enriching of the mediums with ascitic fluid or the adding of a piece of sterile kidney tissue on the bottom of the agar tube involved too much manipulation, such as the pouring of mediums and, therefore, the absorption of oxygen. The addition of 0.2 per cent cysteine hydrochloride to the agar medium provided an anaerobic medium which was easy to prepare and which could be autoclaved. This procedure was suggested by the work of various authors. Quastel and Stephenson, employing casein digest broth, found that cysteine hydrochloride induced the growth of *Clostridium sporogenes* and *Cl. tetanomorphus* in an open tube. Valley²⁸ found that 0.2 cysteine agar was an excellent reducing agent in the medium and thus established favorable conditions for the development of anaerobic organisms.

Criteria for Calling an Organism Anaerobic.—In order to define criteria for aerobiosis, anaerobiosis and facultative anaerobiosis, in connection with the organisms likely to be found in abscess of the lung, the following studies were made:

A drop of twenty-four hour culture of an anaerobic streptococcus (streptococcus Schottmüller) in Smith-Noguchi medium was spread on blood plates, dextrose ascitic fluid agar and plain agar plates. Six plates were used in each case. Half of the plates were incubated anaerobically and half aerobically. The plates were examined in forty-eight hours.

A drop of twenty-four hour culture of an aerobic streptococcus was treated in an identical manner.

The strictly anaerobic organism grows on the surface of plates only under anaerobic conditions. The majority of aerobic organisms grow well on the surface of plates both under anaerobic and under aerobic conditions.

In tubes containing different amounts of broth, the distribution of oxygen in them will not be the same. The surface area of oxygen over the liquid will be smaller, the smaller the diameter of the tube, and the penetration or distribution of oxygen in the tube will be less, the higher the level of fluid. Gates and Olitsky²⁹ found that in a reducing medium such as dextrose broth a column length of from 8 to 16 cm. overlaid with paraffin oil favors the decolorization of methylene blue (methylthionine chloride, U. S. P.). They noted that a column of fluid 8, 10

28. Valley, G.: The Favorable Rôle of Cysteine in the Cultivation of Anaerobic Organisms, *J. Bact.* **17**:12, 1929.

29. Gates, F. L., and Olitsky, P. K.: Factors Influencing Anaerobiosis with Special Reference to the Use of Fresh Tissue, *J. Exper. Med.* **33**:51, 1921.

or 12 cm. long maintained at a constant temperature without agitation practically serves as a seal for the lower levels. Hence, anaerobic conditions can be found on the bottom of the tubes that are narrow enough and that contain sufficient amounts of fluid. Fluid mediums, therefore, are not sufficient criteria for determining whether an organism is anaerobic or aerobic.

It is safe to classify organisms that do not grow on plates aerobically, even under the most favorable circumstances of growth and of mediums, as strict anaerobes. Organisms that fail to grow aerobically on plates seeded with the pus, but which on further subculture grow aerobically, even in slight amount, may be called, for the sake of clearness, "doubtful" anaerobes.

BACTERIAL FLORA OF ABSCESS OF THE LUNG

From studies on the conditions of anaerobic growth, the following routine procedure was adopted as the one best suited to the isolation and study of the anaerobic and aerobic flora.

Procedure for the Cultivation of the Bacterial Flora of Abscess of the Lung.—Pus was obtained at operation in cases of abscess of the lung. The diagnosis of suppuration of the lung was verified by roentgen examination, when feasible by bronchoscopy and later at operation.

Smears of the pus obtained at operation were made and stained by Gram's method in order to determine the type of bacteria. Before culturing, the specimen was examined macroscopically, and the color, odor and consistency were recorded. If the pus obtained was sufficient in amount, blood plates and tubes containing the Smith-Noguchi medium were inoculated and immediately covered with petrolatum seal and incubated at 37.5 C. If only a small amount of pus was obtained, tubes containing the Smith-Noguchi medium were inoculated and then incubated for twelve hours. At the end of this period, the contents of the Smith-Noguchi tubes were centrifugated, the supernatant fluid was discarded, and a blood plate was inoculated with a drop of sediment and spread over the plate with an inoculating brush. Two other blood plates were inoculated with the same brush. This procedure was repeated with another set of two plates. The first set of three plates was placed in a moist jar made anaerobic by the method that I described,³⁰ and then were incubated for from seven to fourteen days at 37.5 C. At the end of this time, the plates were removed from the anaerobic jar, the individual colonies were picked under the microscope, and fresh Smith-

30. Cohen, J.: A Simple Central Catalyzing Station to Produce Anaerobiosis, J. Lab. & Clin. Med. 15:262, 1929.

Noguchi mediums³¹ were seeded as well as in "shake" 1 per cent dextrose agar tubes containing 0.2 per cent cysteine hydrochloride. The colonies in "shake" dextrose cysteine hydrochloride agar were later cut up and seeded in fresh Smith-Noguchi mediums. When pure cultures of organisms were obtained in the fluid medium, fresh blood plates were inoculated and incubated anaerobically and aerobically. Their morphology on fluid and solid mediums, as well as their fermentation on sugars, was studied. The other set of two plates was incubated aerobically at 37.5 C., and these were examined after twenty-four and forty-eight hours.

Bacterial Flora; Streptococcus.—In all of the cases studied, *Streptococcus nonhaemolyticus* (Gamma-Brown) was found. This organism was a "doubtful" anaerobe. In one case a strictly anaerobic streptococcus was isolated which gave off a fetid odor with gas in fluid mediums containing dextrose. This organism corresponded in all its properties to *Micrococcus foetidus* (Veillon), which will be described. In all other cases a streptococcus that did not grow aerobically at first and that grew only after the second or third subculture on plates was isolated.

Cultural Characteristics of Streptococcus-Gamma Commonly Isolated from Cases of Suppuration of the Lung.—This organism proved to be the easiest of all the organisms encountered in this study to isolate and to maintain in culture. While the majority of the organisms isolated from abscesses of the lung often failed to grow in culture even in the richest anaerobic mediums, it was always possible to isolate the "doubtful" anaerobic streptococcus. Another interesting feature was the influence of aerobic and anaerobic conditions on its growth on the surface of plates.

EXPERIMENT 1.—Smith-Noguchi medium was inoculated with pus obtained at operation and incubated for twenty-four hours at 37° C. At the end of this period, a drop of culture was spread on four blood plates and on four ascitic fluid agar plates. Half of the plates were incubated anaerobically and half aerobically. The Smith-Noguchi culture was left in the incubator for two, four and seven days. At the end of two days, a drop of the same culture was poured on the same number of plates, and these plates were incubated anaerobically and aerobically. In four days, and again in seven days, the same process was repeated.

The "doubtful" anaerobic streptococcus grew on all anaerobic plates, irrespective of the age of the culture. Growth on aerobic plates was obtained only with the two days old cultures.

EXPERIMENT 2.—The first subculture on anaerobic plates was again subcultured on plates and incubated under anaerobic and aerobic conditions; whenever there was growth on the plates incubated aerobically, the growth was again subcultured on plates and incubated under anaerobic and aerobic conditions.

31. Repeated experiments have shown that when colonies of anaerobic organisms are seeded into large Smith-Noguchi tubes growth is less frequent than when the same colonies are seeded into tubes 10 by 1 cm. containing from 1 to 2 cm. of Smith-Noguchi medium.

There was growth on anaerobic plates whether the organism was subcultured from either anaerobic or aerobic plates. Growth aerobically on plates was obtained only when the organism was subcultured from an anaerobic plate and not from an aerobic one.

As is seen from experiments 1 and 2, an anaerobic environment is conducive to aerobic growth of certain "doubtful" anaerobic organisms and has a protective effect on them. Thus the organisms which were grown anaerobically grew both anaerobically and aerobically in subculture; but the organisms which had already grown aerobically and possibly were injured by exposure to the air grew anaerobically only in subculture. This phenomenon was not observed among all of the strains studied.

Growth: On plates the colonies are humid, round dewdrops which by transmitted light appear gray, glistening or opaque. They do not produce hemolysis on the blood plate. Good granular growth is obtained in both plain bouillon and 1 per cent dextrose broth. Organisms grow with a flocculent deposit on the bottom of the Smith-Noguchi tube, without the production of gas.

Fermentation of Sugars: As a rule, dextrose, saccharose and maltose were fermented. The remaining sugars, lactose, inulin and mannite, were fermented by some and not by others. Gelatin was not liquefied, and litmus milk was coagulated, with the production of acid in only four cases.

Agglutination: An attempt was made to find out whether these organisms belonged to a common serologic group. Streptococcus from one case (that of H. F.) was employed as an antigen to immunize rabbits, and immune serums were obtained. Rabbits were immunized the first two weeks by intravenous injections of increasing doses (from 1 to 12 cc.) of a saline emulsion of organisms killed at 60 C. for one hour, followed the third and fourth weeks by injections of increasing doses (from 1 to 12 cc.) of a saline emulsion of live organisms. The immune serums were tested against the strains of organisms isolated. While the homologous strain was agglutinated by its immune serum in the dilution of from 1:10 to 1:1,200 the various strains of streptococci isolated from abscess of the lung were not agglutinated by this serum.

From the foregoing data it is seen that the streptococci isolated did not give the same reactions to sugar, nor did they belong to the same serologic group.

Pathogenicity: Streptococci were not pathogenic to rabbits and guinea-pigs when from 1 to 2 cc. of a twenty-four hour culture in Smith-Noguchi medium was injected intravenously, and also locally, into the skin. When 0.5 cc. of this culture was injected intratracheally into

the bronchus of a dog by means of a bronchoscope,³² a localized pneumonitis usually followed.

In view of the fact that a strictly anaerobic streptococcus had repeatedly been reported by various observers in abscess of the lung, the question arose as to whether the pus contained a mixture of a strict anaerobe and of a doubtful anaerobe, the latter overgrowing the strict anaerobe. The method of isolating a single bacterial cell with Chambers' apparatus was tried, in order to separate these two types of organisms. A few of the organisms were isolated by this method; they were grown and studied, but they finally grew aerobically.

An organism which on spread appeared to be *Streptococcus micros* was observed in some of the cases, but could not be identified culturally.

Diphtheroids.—Various types of gram-positive bacilli and coccobacilli were isolated which morphologically were pleomorphic and strongly suggestive of diphtheroids. A coccoid form appeared as a streptococcus, but gave off gas in fluid mediums containing dextrose; there was a small, stubby, bacillary form, and still another form was thick and somewhat curved, with rounded ends, about the size of the diphtheria bacillus. In their cultural characteristics these forms behaved like the "doubtful" anaerobic streptococcus, except that, unlike the streptococcus, they produced gas with an acrid odor in mediums containing dextrose (the odor could be easily differentiated from the one obtained in culture of *M. foetidus*, *Strep. putridus* and *Strep. anaerobius*). Not unlike the streptococcus, they varied in their reactions on sugars and coagulated milk and they did not liquefy gelatin.

In one case a small coccobacillus with pointed ends was isolated, which proved to be a strict anaerobe. On blood plate, it grew anaerobically as a small, opaque, granular colony with a raised center. After prolonged incubation in an anaerobic jar, the colony, on a blood plate, appeared as a homogeneous, round ball on top of a granular irregular surface. It was sharply outlined, moist and dome-shaped. In broth with a petrolatum seal, it grew half-way down the tube, with cloudiness of the mediums and a granular gray deposit on the bottom. In dextrose broth plus petrolatum seal, it grew, and there was a slight cloudiness of the mediums, with a granular gray deposit on the bottom and some production of gas. The greatest amount of gas was evolved in the Smith-Noguchi medium, with the evolution of a sharp acrid odor. Stab cultures in plain and dextrose agar remained sterile. The organism fermented dextrose, saccharose, lactose, maltose, inulin, mannite with acid and gas. It coagulated milk and did not liquefy gelatin.

32. Dr. Rudolph Kramer, of this hospital, performed the bronchoscopy on the dogs.

Micrococcus Foetidus (Veillon).—In one case a strictly anaerobic organism simulating *Micrococcus foetidus* was isolated. A description is given by Veillon. The following additional properties were observed. On blood plate, the colonies appeared round and dome-shaped, with a corrugated border. In fluid mediums, the organism occurred in pairs and in chains, giving off a characteristically fetid odor.

B. Ramosus.—This organism was isolated and described by Veillon and Zuber as a strict anaerobe. It is a small, slender bacillus with a cylindric and ovoid enlargement like the diphtheria bacillus. It has no spores; branching was noted by Veillon and Zuber. It stains feebly with Gram's stain. This organism coagulates milk and does not grow in gelatin. All cultures give off a peculiar fetid odor.

The following additional properties were found in connection with the organism. It retained the Gram stain. In culture, it was the size of a diphtheria bacillus; in pus, it appeared like needles of fir. On blood plates, it appeared as a small, round, opaque, yellowish-gray, raised, mucoid, glistening colony with regular edges. In bouillon plus petrolatum seal, growth appeared on the third or fourth day as a grayish granular deposit on the bottom with very slight general turbidity; there was no gas; the same character of growth was observed in dextrose broth. In the Smith-Noguchi medium, growth appeared as a flocculent deposit on the kidney tissue with a general turbidity plus a great deal of gas and a fetid odor (the odor is different from that given off by diphtheroids). After twenty-four hours, agar stab showed a flaky growth along the line of stab. After five days, dextrose agar stab showed a microscopic, pinpoint, translucent growth below the surface of the agar. On milk, gas was evolved, but the milk was not coagulated. Gelatin was not liquefied and showed a flocculent deposit about the kidney tissue. In ascitic fluid, sugar mediums, inulin, mannite and saccharose were fermented. In Hiss' serum water sugar mediums, saccharose and mannite also were fermented.

B. Melaninogenicum.—This organism is a strictly anaerobic, gram-negative bacillus; it was first described by Oliver and Wherry,³³ and later, more fully, by Burdon.³⁴ It was found to be a small, pleomorphic, slightly curved, thin, nonmotile, gram-negative, nonacid-fast rod with pointed ends. Large forms were also noted in pus and culture. It grew in symbiosis with the streptococcus, and it was difficult to isolate the bacillus in pure culture, but it grew well with the streptococcus. On blood plate it produced a black, extracellular pigment, melanin; the blood pigment disappeared from the plate and left the agar transparent.

33. Oliver, W. W., and Wherry, W. B.: Notes on Some Bacterial Parasites, J. Infect. Dis. **28**:341, 1921.

34. Burdon, K. L.: *B. Melaninogenicum* from Normal and Pathogenic Tissues, J. Infect. Dis. **42**:161, 1928.

The organism isolated in this laboratory was found to conform to this description and to possess the following additional properties: In pus, from lesions produced by injecting this organism intratracheally into the lungs of rabbits, the organism appeared in the shape of a coccobacillus. On blood plates, young colonies appeared with flat irregular borders and a raised center. Older colonies appeared as large, homogeneous, gelatinous, glistening mounds with irregular circinate borders; there was coffee-black amorphous material on top of the mound. The property to produce black pigment on a blood plate was lost in subculture whether from solid or from fluid mediums. Subcultures on a blood plate appeared as flat, round, regular, dry, darkly frosted, adhering, hemolytic colonies. The colonies appeared in from seven to fourteen days; rarely they appeared in two or three days. In fluid and also in solid mediums, the organism gave off a peculiar fetid odor. Gas was evolved in abundance in fluid mediums. It grew in symbiosis with the streptococcus gamma, a "doubtful" anaerobe, which in many instances failed to grow aerobically on plates, and therefore behaved like a strict anaerobe. In the Smith-Noguchi medium there was a slight general turbidity, with a greenish-black, flocculent deposit on the bottom and a great deal of gas and odor. No growth appeared in agar stab or in dextrose agar stab. A faint grayish deposit in the bottom of the tube appeared within from four to five days in plain and in dextrose broth when these were sealed with petrolatum. In gelatin, the growth appeared as a diffuse, blackish-gray deposit over the kidney tissue. Gelatin was not liquefied. In litmus milk the growth produced acid and gas. Milk was not coagulated. In ascitic fluid sugars there was no growth. In Hiss' serum water sugars there was slight growth. In dextrose, maltose and lactose the organism grew, with the production of acid. There was no growth in other sugars. The organism was fragile, and cultures became sterile after the fourth or fifth subculture. The addition of 1 cc. of 10 per cent gum arabic in 1 per cent dextrose broth revived the organism for further growth.

B. Furcosus.—This organism is a strictly anaerobic, small, gram-negative bacillus with rounded ends; it is slightly curved and has knob-like projections or piriform swellings at one end. It is somewhat thicker than *B. tuberculosis*; it is a nonspore bearer and is nonmotile. On the surface of agar, colonies appear like colonies of pneumococci.

The following additional properties were noted: In Smith-Noguchi medium there was a fine granular growth along the side of the tube, with the evolution of gas and a fetid odor. The production of gas was not lost in subculture. On the surface of the blood plate, it appeared as a round, dull, granular, moist colony, with a somewhat irregular, slightly raised dentate border. Younger colonies appeared like a small shirt button with a central depression. Older colonies had the appear-

ance of a stump of a tree with concentric circles. When grown in symbiosis with streptococcus, the colony had a varied granular deposit on its surface. Gas was not produced in broth or in dextrose broth. Gas was produced in dextrose, maltose, saccharose and mannite. It was not produced in lactose and inulin. Milk was not coagulated, and gelatin was not liquefied.

B. Thetoides.—A description of this organism is given by Besson.³⁵ It is a strictly anaerobic, gram-negative bacillus, with rounded or pointed ends; it is nonmotile and is a nonspore bearer. It appeared like a safety-pin, because of granules at either one or both ends, and of vacuolation in the middle of the cytoplasm. These granules were gram-negative. It was the size of the diphtheria bacillus, but was somewhat thicker. Occasionally larger forms were noted.

The following additional features were noted: In Smith-Noguchi medium the growth was characterized by a profuse cloudiness of the medium and a flocculent, stringy deposit on the bottom, with the evolution of gas and a fetid odor. Bouillon culture covered with petrolatum showed a granular deposit on the bottom. Dextrose, saccharose, maltose, lactose, mannite and inulin were fermented, with the evolution of gas. Litmus milk was coagulated and acidified. Gelatin was liquefied.

B. Fragilis.—This organism is a strictly anaerobic, tiny, gram-negative coccobacillus; it is nonmotile, is a nonspore bearer and is not acid-fast. On the surface of agar colonies were transparent, grayish-like colonies of pneumococci. The deep agar colonies were yellowish brown. The organism was very fragile.

The following additional properties were noted: On the blood plate, the colonies appeared as homogeneous, grayish, glistening mounds surrounded by a granular, tiny, scattering, needle-shaped border. By direct light, the colonies were hardly visible and were humid and transparent. In Smith-Noguchi medium, there was a generalized turbidity; the organism usually grew about from $\frac{1}{2}$ to 1 inch (1.2 to 2.5 cm.) from the petrolatum seal, with a moderate amount of gas with a fetid odor. There was no precipitate over the kidney tissue. Gas was not produced in subculture. There was no growth in plain or in dextrose broth. The organism fermented maltose, dextrose, saccharose and lactose. Mannite and inulin were not fermented. Litmus milk was not acidified, and gelatin was not liquefied.

Staphylococcus Parvulus.—A full description of this organism is given by Veillon and Zuber, and quoted by Ford.³⁶

35. Besson, A.: Practical Bacteriology, Microbiology and Serum Therapy, translated by H. J. Hutchens, New York, Longmans, Green & Company, 1913, p. 572.

36. Ford, W. W.: Text-Book of Bacteriology, Philadelphia, W. B. Saunders Company, 1927, p. 451.

The following additional features were noted: On the blood plate, the colonies appeared glistening, humid, dome-shaped and microscopic. In Smith-Noguchi medium, the organism grew as a slight gelatinous growth on the bottom of the tube under the kidney tissue, with no production of gas; the generalized turbidity was slight.

B. Fusiformis.—A full description of this organism is given by Ozaki, and quoted by Ford.³⁷

The following additional features were noted: The organism is strictly anaerobic and gram-negative, with pointed ends and with fusiform bulging in the middle which holds two gram-positive bands. On blood plates, the colonies appeared as granular, round depressions (nucleus) in the middle of a pyramidal, irregular border. The growth was gray, mucoid, viscid and translucent and gave the appearance of piled up mucus. In Smith-Noguchi medium, the growth appeared as a greenish-black, gelatinous precipitate on the bottom of the tube over the kidney tissue, with a homogeneous slight cloudiness of the medium and the evolution of gas and a fetid odor. In subculture to the Smith-Noguchi medium, there was the same greenish-black precipitate, but the medium was clear. In plain broth with a petrolatum seal, there was a small granular deposit on the bottom of the tube with some gas and with slight cloudiness of the medium. The same type of growth was produced in dextrose broth. Acid and gas were produced in Hiss' sugars (dextrose, maltose, saccharose and mannite). Acid alone was produced in lactose and inulin. Gelatin was not liquefied. Gas and acid were produced in litmus milk.

Leptothrix.—A full description of the properties of this organism is given by Oliver and Wherry.³⁸

The following additional features were noted: The organism is strictly anaerobic, gram-negative and threadlike, with gram-positive granules, appearing as streptococci. On the blood plate, the colonies were bizarre, with branching, a piled up center, irregular, finger-like projections and a corrugated border of the periphery (a Medusa-like colony). The growth appeared greenish by reflected light, and was mucoid gray by direct light. In Smith-Noguchi medium, there was generalized turbidity with the evolution of gas and a fetid odor. Hiss' sugars (dextrose, maltose, lactose, saccharose, mannite and inulin) were fermented, with the evolution of gas. Gelatin was not liquefied. Litmus milk was acidified and not coagulated.

Vibrio.—Anaerobic *Vibrios* were isolated by Muhlens, Veillon and Repaci from ulcerating lesions in tuberculosis of the lungs, by Soper

37. Ford (footnote 26, p. 288).

38. Oliver, W. W., and Wherry, W. B.: *Leptothrix Innominata*, J. Infect. Dis. 19:299, 1916.

from pericardial effusion and by Tunncliffe from sputum in a case of acute bronchitis. A description of the properties of these organisms is given by the various authors.

The following properties were found to be possessed by the organism: It is a strictly anaerobic, gram-negative, curved, nonspore bearing organism; it appears singly or in bunches. On the blood plate, it appeared as a yellow, viscid, round, gelatinous mass. In Smith-Noguchi medium, it grew with diffuse cloudiness of the medium, with a gelatinous deposit on the bottom of the tube. There was a moderate amount of gas and some odor. Acid and gas were produced in lactose and saccha-

*Type of Organisms Isolated in Sixteen Cases of Abscess of the Lung**

Name	Streptococcus Gamma	Diphtheroids	B. Melanogenicum	B. Fusiformis	B. Ramosus	B. Fragilis	B. Furcosus	B. Thetoides	Str. Parvulus	Leptothrix	Vibrio	Other Anaerobes	Anaerobic Organisms
A. R.	+	+	+	+	Cl. cochlearum
W.	+	+	+	+	+
C. G.	+	+	..	+
H. F.	+	+	+	..	+
D. R.	+	+	+	..	+	+	+	..	+	B. friedländeri
N. D.	+	+	+	+	+	+	+	+	+	+	+
R.	+	+	+	+
F. L.	+	+	+
S. D.	+	+	+	+	+
S.	+	+	+	..	+	+
B. J.	+	+	+
E.	+	+	+	Str. viridans
B. L.	+	+	+	+
R. M.	+	+	+	+
M. R.	+	+	+	+	+	Str. viridans
K.	+	+	+	+

* The pus was obtained at operation.

rose. Acid was produced in maltose, mannite and dextrose. There was no growth in litmus milk and in gelatin.

Other Organisms.—Of the other anaerobic organisms isolated, *Clostridium cochlearum* was isolated in one case.

Of the aerobic organisms isolated, *B. friedländeri* was isolated in one case, and *Strep. viridans* in two.

SUMMARY AND CONCLUSIONS

As is seen from the accompanying table, in sixteen cases of abscess of the lung in which pus was obtained at operation, the "doubtful" anaerobic streptococcus and the diphtheroid were found in every case. *B. melaninogenicum* was found in fourteen cases, *B. fusiformis* in six, *B. ramosus* in eight, *B. fragilis* in five, *B. furcosus* in two, *B. thetoides* in three, *Staph. parvulus* in two, *Leptothrix* in three, *Vibrio* in one, *M.*

foetidus in one and *Cl. cochlearum* in one. Of the aerobic organisms, *B. friedländeri* was found in one case and *Strep. viridans* in two cases. It is seen, therefore, that the three organisms most commonly found in abscess of the lung were *Strep. gamma*, diphtheroid and *B. melaninogenicum*.

The flora is rich and varied and seems to occur in combinations of organisms. In the sixteen cases of abscess of the lung studied, in which pus was obtained at operation, streptococcus, diphtheroid and *B. melaninogenicum* were found in fourteen cases. In addition to the last three organisms, *B. fusiformis* was also found in five cases, making one combination; *B. ramosus* was found in another five cases, making another combination, and *B. fragilis* was found in still another five. Noteworthy, also, was the close symbiosis of the two organisms most commonly found in abscess of the lung, *Streptococcus gamma* and *B. melaninogenicum*. These facts raise the question whether this combination of organisms has a bearing on the etiology of abscess of the lung. This work will be the subject of another report.

THE INTRA-ABDOMINAL METHOD OF REMOVING INGUINAL AND FEMORAL HERNIA *

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Whatever else may be necessary as a part of the operative procedure for the cure of hernia, complete removal of the sac followed by high ligation or suture of the peritoneum is essential. All surgeons recognize this as the most important part of the procedure and many believe that in small-sized indirect hernias in children and young persons success is apt to follow regardless of the method employed for closing the canal. For hernias of large size, for direct hernia with imperfect development or absence of the conjoined tendon and for postoperative rupture, it is necessary to suture together certain fascial structures, such as the conjoined tendon and the shelf of Poupart's ligament. In many cases the use of fascial strips as recommended by Gallie is extremely important.

The numerous modifications of the original operations of Bassini and of Halsted have been directed largely, if not solely, to methods of closure of the canal and wound.

The old operative procedure consists of dissecting out the hernia from below, brushing off the anatomic coverings of the hernial sac, until it is clearly evident that the portion of the peritoneum above the neck of the sac is clearly exposed and ligated or sutured.

Surgeons of great skill are accomplishing this regularly in ordinary cases of hernia, and are succeeding in curing hernia in a high percentage of cases. Failures under the name of "recurrent hernia" in the hands of the best surgeons have amounted to no less than 5 per cent, and frequently after one or two years it will be found that in from 10 to 20 per cent of patients the result is a failure, i. e., a "recurrence."

Even in hernias of small size, when the dissection of the sac is performed from below through the inguinal canal, there is of necessity some injury to the cremaster muscle and fascia, and the line of cleavage between the peritoneal sac and the surrounding structures may not always be easily determined. In long-standing hernias of large size, the process of dissecting out the sac is tedious and may be difficult; the line of cleavage may be found only with the greatest difficulty, and all the time this is being done the inguinal canal is being greatly enlarged, surrounding structures traumatized, and important structures injured.

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* From the Department of Surgery, Medical College of Virginia.

In previous contributions I have described a method of approach for removing the sac of inguinal and femoral hernia from within the abdominal cavity. I am presenting now some improvements as gradually developed from experience in using the method in more than 1,700 cases.

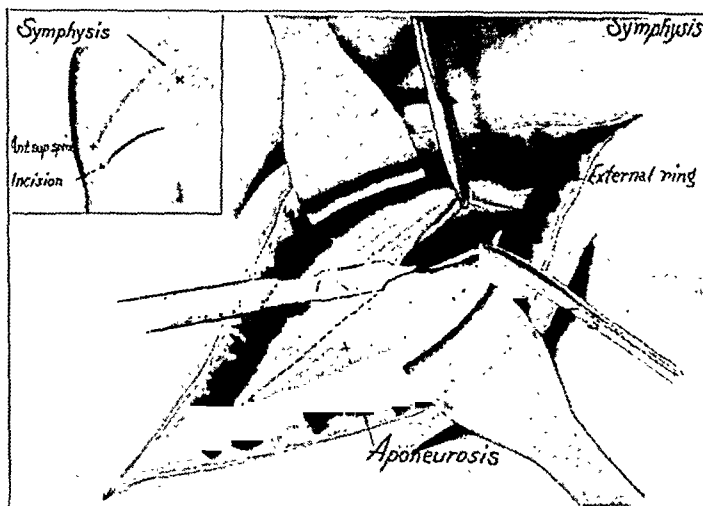


Fig. 1.—Operation for hernia, seen from the abdominal side. The incision is being made through the aponeurosis. The insert shows the skin incision.

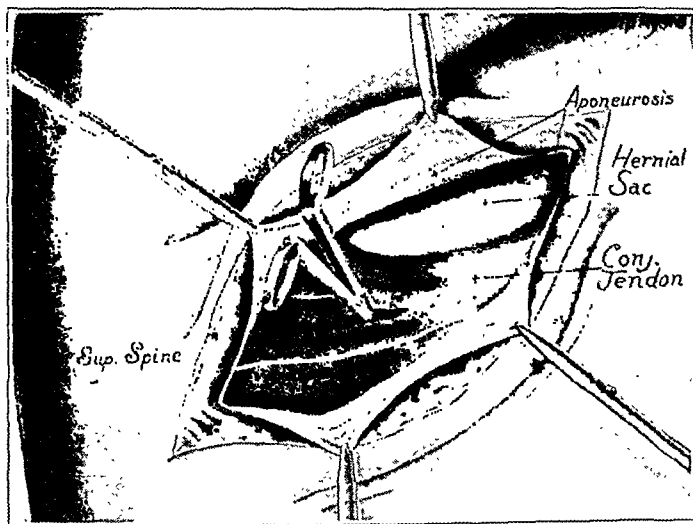


Fig. 2.—Operation for hernia, seen from the abdominal side. The fibers of the internal oblique are being separated well above the neck of the sac.

Many surgeons are recognizing the advantages of this method of approach in the treatment for hernia, and it is being employed with various modifications extensively. In observing other surgeons attempt the operation, I note that they either have failed to comprehend the

main points or have so modified the important technical parts of the procedure as to impair greatly the usefulness of the method.

For this reason, I have had a new series of illustrations made, which I hope may more accurately depict the operative procedure.

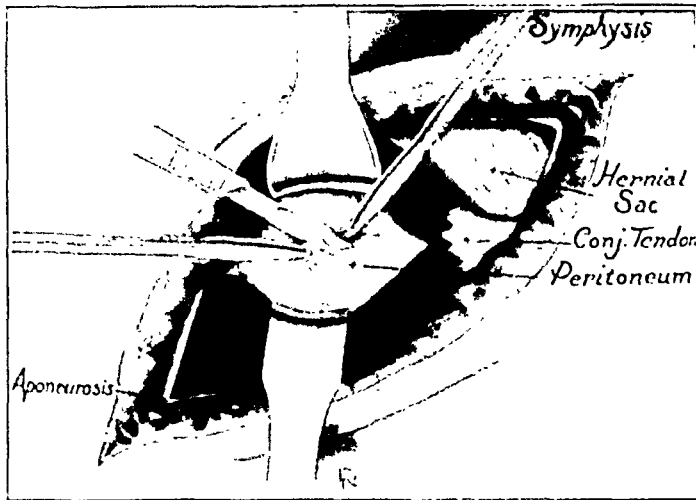


Fig. 3.—Operation for hernia, seen from the abdominal side. The peritoneum is being opened, about an inch above the neck of the sac.

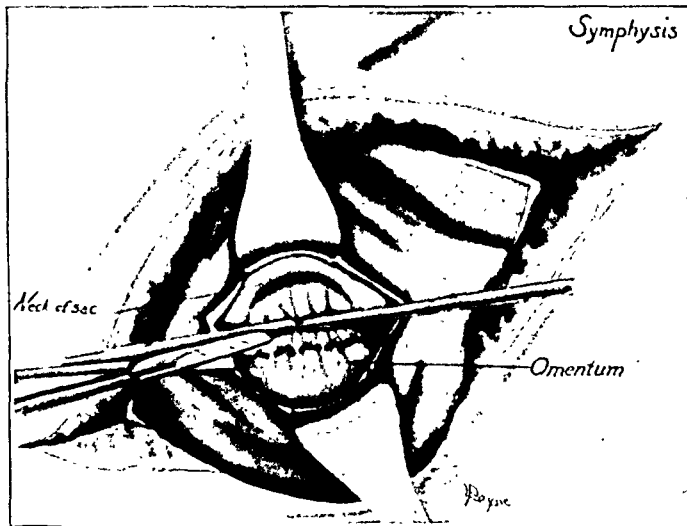


Fig. 4.—Operation for hernia, seen from the abdominal side. The omentum incarcerated in the hernial sac is ligated and cut, leaving the incarcerated portion in the sac.

The usual hernia incision is made, perhaps slightly higher than usual, the aponeurosis of the external oblique is exposed and divided as in the ordinary operation. The muscle fibers of the internal oblique

and the transversalis are separated, and the peritoneum is opened just as if an appendectomy were going to be performed.

From the peritoneal side it is easy to recognize and distinguish between hernia into the inguinal and femoral canals, direct and indirect

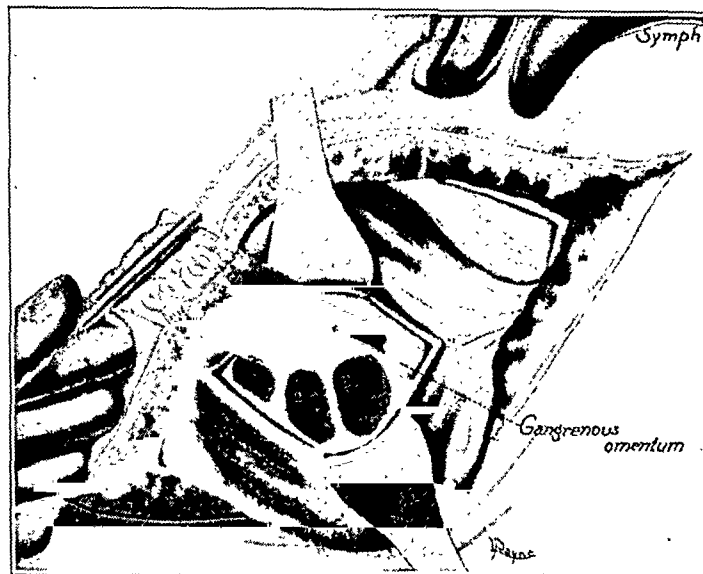


Fig. 5.—Operation for hernia, seen from the abdominal side. Gangrenous omentum is being pulled from above out of the hernial sac.

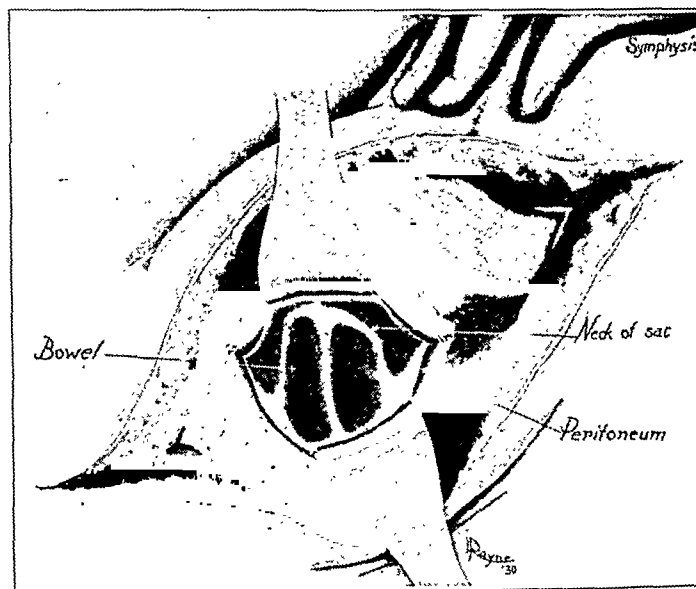


Fig. 6.—Operation for hernia, seen from the abdominal side. Two loops of bowel are incarcerated in the sac of the inguinal hernia.

inguinal hernia, unusual and anomalous types of hernia, the amount of redundant peritoneum and preperitoneal fat in and about the canal, the exact location of the bladder, vas deferens and important vessels, and whatever complications may exist.

In cases of strangulated or incarcerated hernia and of hernia with an anomalous type of sac, it needs little discussion to see the advantages of an approach from above. Incarcerated and adherent structures are safely separated from the hernial sac; restoration of circulation in the bowel

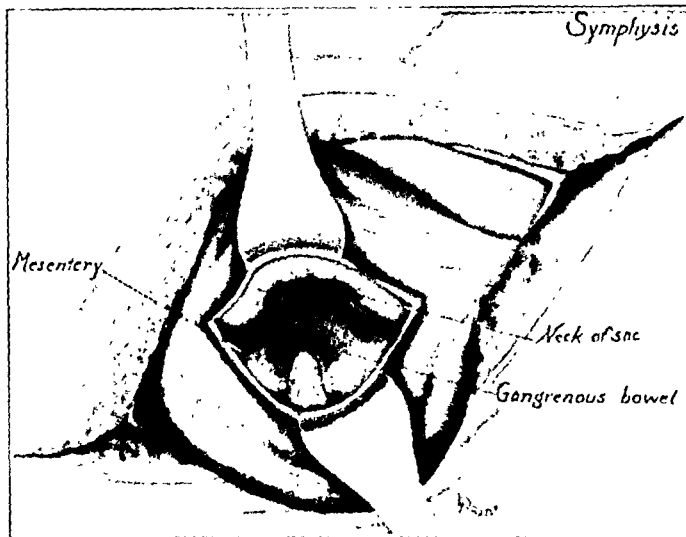


Fig. 7.—Operation for hernia, seen from the abdominal side. Strangulated bowel is returned out of the sac into the peritoneal cavity to be observed for restoration of normal color.

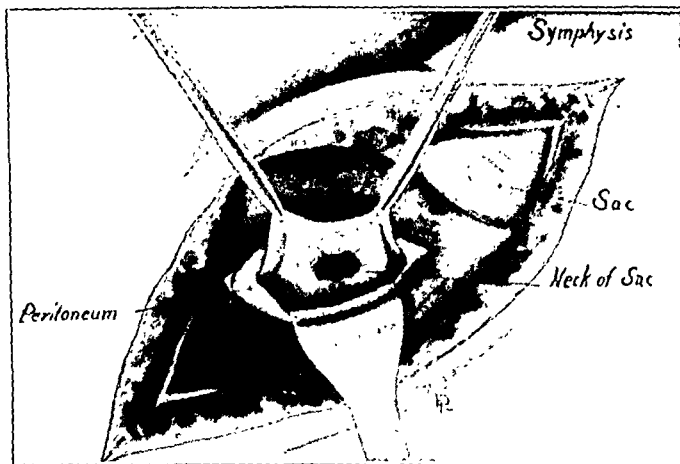


Fig. 8.—Operation for hernia, seen from the abdominal side. The peritoneal cavity is open and the neck of the hernia and surrounding peritoneum are seen from within the abdominal cavity.

occurs more promptly with the bowel free in the peritoneal cavity and the vessels free from traction; ligation and removal of omentum and resection of gangrenous bowel are more safely done under good

exposure; and coincident pathologic changes in the region of the hernial orifice may be recognized and dealt with if desired.

Dissection of the sac is greatly facilitated by enucleation from above, beginning in the natural line of cleavage between the peritoneum and its

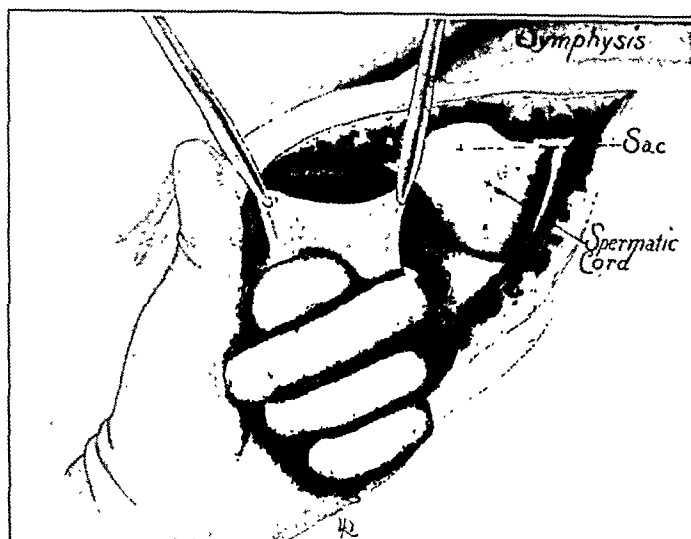


Fig. 9.—Operation for hernia, seen from the abdominal side. The finger is inserted into the hernia through its neck from the abdominal side.

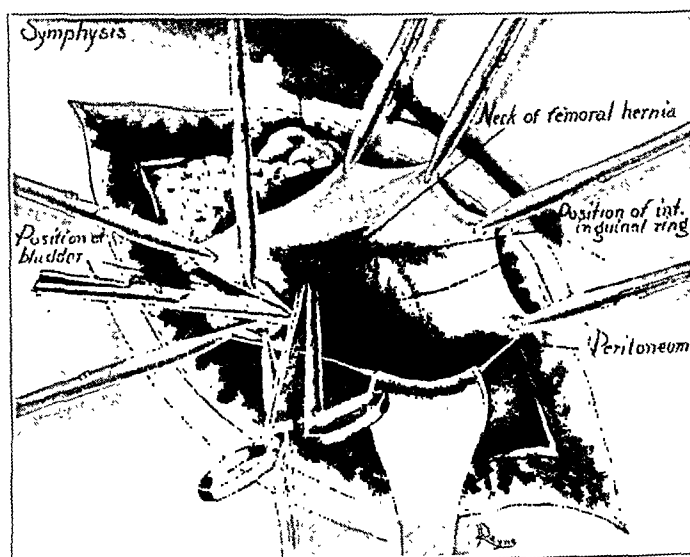


Fig. 10.—Operation for hernia, showing a femoral hernia from the abdominal side. The redundant peritoneum is being incised preliminary to removal of this and the sac of the hernia from within the abdominal cavity in exactly the same way as if it were an inguinal hernia.

nonadherent coverings above the neck. The line of cleavage is easily found; enucleation downward in the natural direction beneath the fascia is done with little trauma to the cremaster, internal oblique and other

muscles of the region. The bladder and structures of the cord, continuously in view, are gently brushed away and preserved from injury as enucleation proceeds. After removal of the sac, suture of the peritoneum is made at a point as high as desirable, sometimes 2 or 3 inches

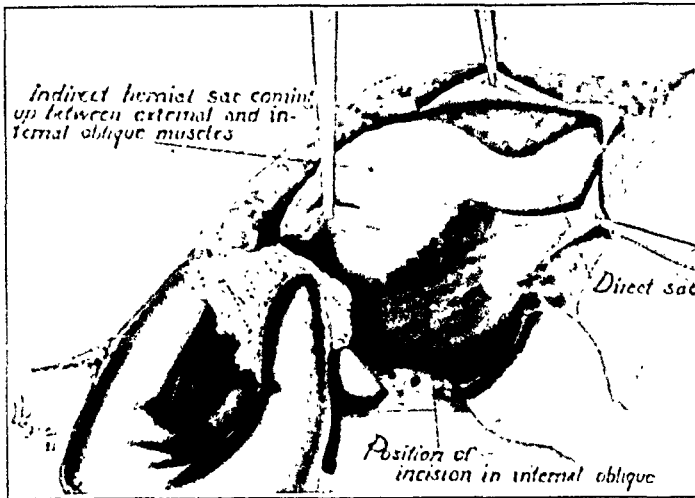


Fig. 11.—An interparietal (interstitial) hernia with a double "pantaloon" type of sac. The direct sac is in the inguinal canal; the indirect sac is between the aponeurosis and the internal oblique muscle. The aponeurosis has been split; both sacs are shown, the dotted line indicating the position of the muscle-splitting incision in the internal oblique.

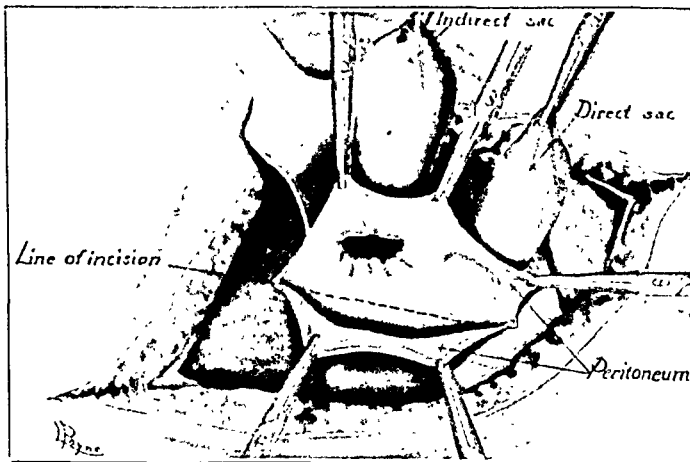


Fig. 12.—The peritoneal cavity is open, showing the openings of both sacs, and the sacs lifted up on forceps.

(5 or 7.6 cm.) above the original location of the neck of the hernia, and if one chooses, by catching the transversalis fascia the peritoneal suture is fixed to a higher position.

Whatever plastic procedure may be the preference of the individual surgeon, or may be the most suitable for the individual case, may be

employed in closing the canal and wound, and one is certain at the conclusion of the operation that the hernial sac is completely removed; and unless serious infection of the wound occurs postoperative rupture will not follow.

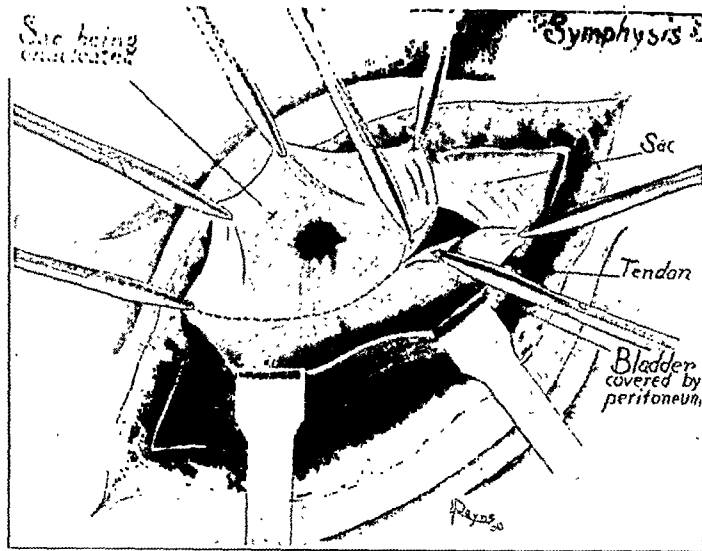


Fig. 13.—Operation for hernia, seen from the abdominal side. Redundant peritoneum for about an inch around the neck of the hernia is being dissected preliminary to enucleation of the sac. This shows the bladder, vas deferens and spermatic vessels safe from injury.

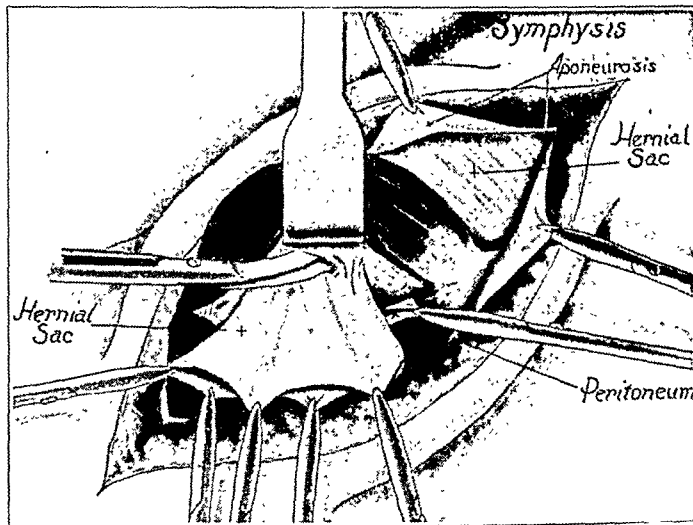


Fig. 14.—Operation for hernia, seen from the abdominal side. The lower edge of the peritoneum, being pulled upward, is easily enucleated after the insertion of blunt scissors into the space between the peritoneum and the overlying fascia.

At this point I would caution against the employment of certain modifications which I have seen other surgeons use. Instead of making the small muscle split incision for exposure of the peritoneum an inch

above the hernial orifice, one might be tempted to hook his finger or a retractor under the arching fibers of the internal oblique, and forcefully pull the muscles up to the point at which it is desired to open the peri-

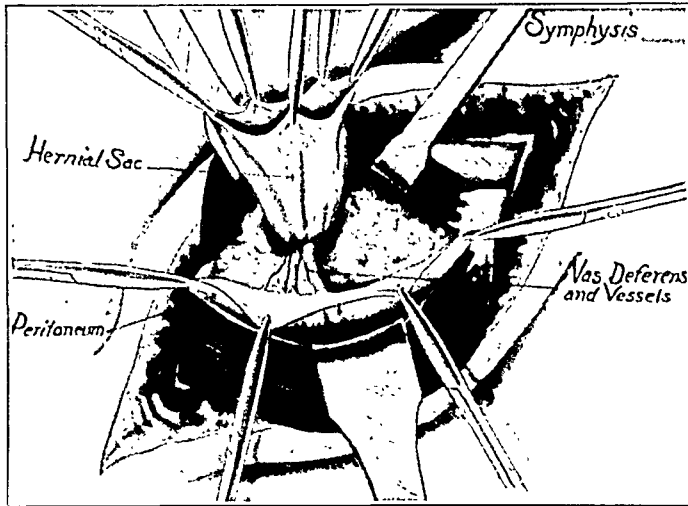


Fig. 15.—Operation for hernia, seen from the abdominal side. The sac, being pulled upward out of the inguinal canal, is easily separated from the vessels and vas deferens, beginning from the abdominal side.

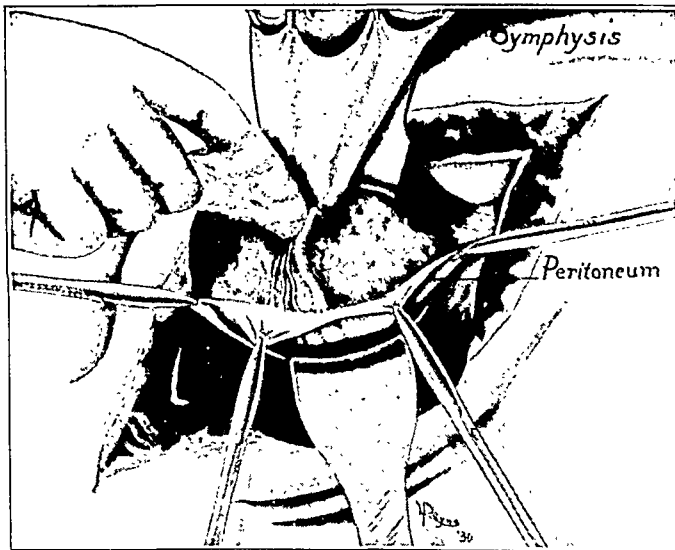


Fig. 16.—Operation for hernia, seen from the abdominal side. Aided by the gauze-covered finger, enucleation of the sac is almost completed and the vas and vessel are gently brushed away from the sac.

toneum, thus greatly overstretching the inguinal canal and seriously injuring the muscles of this region.

Others have been content, after making the muscle split incision and opening the peritoneal cavity, to suture the upper edge of the peritoneal

incision to the peritoneum behind the hernial orifice, without making any attempt to remove the sac. One might be tempted to do this in small children in whom hernia often is cured spontaneously, and in certain cases in which the patient is desperately sick with strangulated hernia.

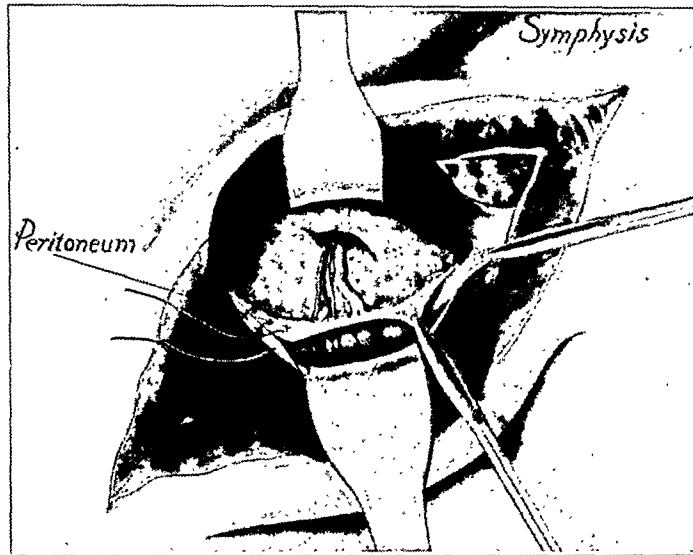


Fig. 17.—Operation for hernia, seen from the abdominal side. The sac has been completely removed from above downward, through an easy line of cleavage, leaving the fascia, vessels, vas and fat in situ uninjured. The cut edges of the peritoneum are being sutured.

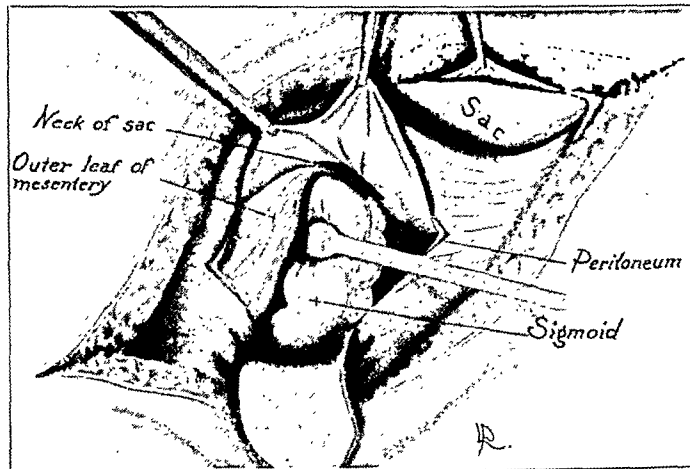


Fig. 18.—Sliding hernia of the sigmoid seen from within the abdominal cavity. Note that the bowel passes into the inguinal canal behind the sac, the neck of which is shown as a slitlike opening because it is lifted up by the sigmoid.

But no one should be deceived into believing that he has actually cured a hernia until the sac has been at least permanently separated from the peritoneal cavity by complete division at the highest portion of the neck, followed by ligation or suture of the peritoneum.

It is not my intention in this contribution to discuss the old question of "recurrences." It is better to discard the word "recurrence" and substitute for it "failure." Failures are of two types: (1) separation of the edges of the original incision at the point of ligation of the sac

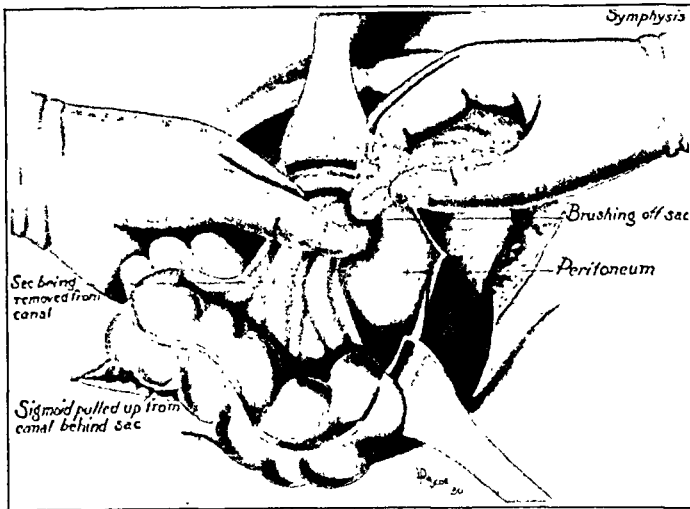


Fig. 19.—Operation for hernia, seen from the abdominal side. This shows a sliding hernia of the sigmoid after the sigmoid has been pulled out of the inguinal canal through an incision into the peritoneal cavity after splitting the muscles of the internal ring. The sigmoid has already been pulled out of the canal, and the sac is now being pulled out.

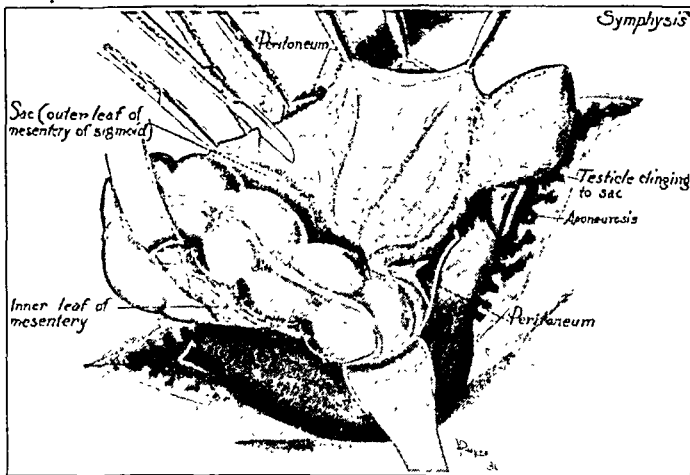


Fig. 20.—The sac of the sliding hernia, together with the outer leaf of the mesentery of the sigmoid is about to be removed by scissors dissection.

(rupture); (2) the overlooking, at the primary operation, of part of the original hernia proximal to the point of original ligation of the sac or the presence of another leg of the pantaloons type of hernia—usually the direct variety. Such sacs or proximal portions of the original sac

of course are not likely to be overlooked when careful surgeons are operating on hernias according to the method described here.

No statistical study of "recurrent hernia" can be made to tell the whole truth, and statistics can be made to conceal anything, even the

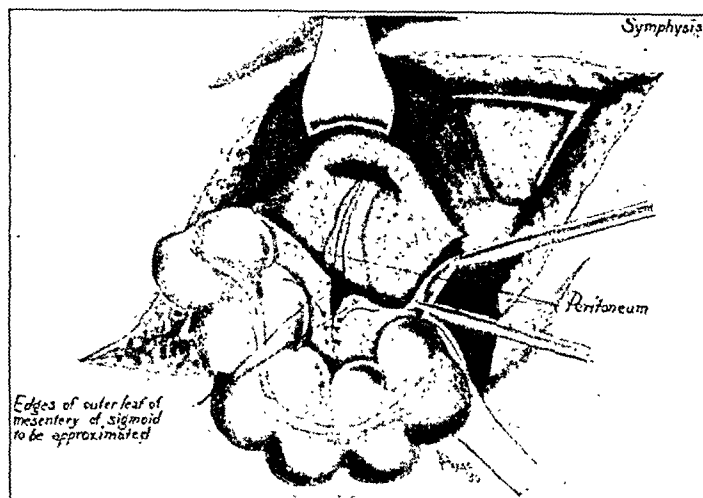


Fig. 21.—Operation for hernia, seen from the abdominal side. The sac of the sliding hernia, together with the outer leaf of the mesentery of the sigmoid has been removed, and the edges of the mesentery are being sutured together until the proper level is reached preliminary to closing the peritoneal cavity. The inguinal canal transmitting the vas and vessels is seen.

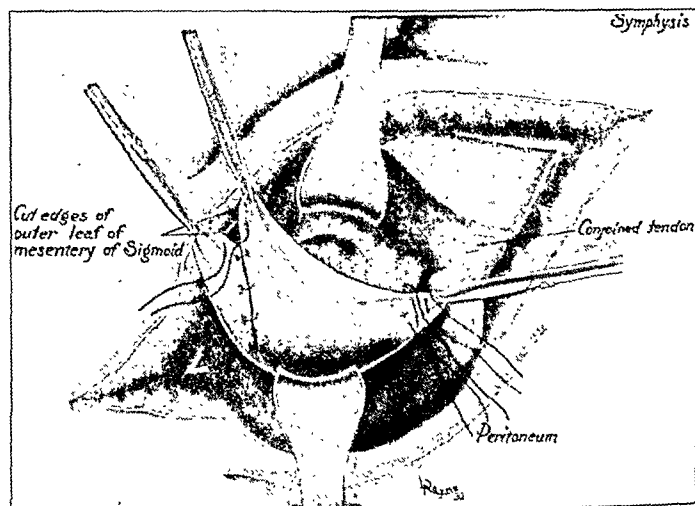


Fig. 22.—Operation for hernia, seen from the abdominal side. The outer leaf of the mesentery is completely sutured, and the two edges of the original incision into the peritoneal cavity are now being closed.

truth. The value of any method of operating for any disease cannot be determined with accuracy from statistics alone. If the procedure is based on sound principles, successes and failures are representative rather of the surgeon than of the method. Skilful surgeons often have

success with poor methods; amateurs and careless operators have a large number of failures by all methods.

For many years I have made painstaking efforts to examine the patients from time to time, to determine the number of failures. A large

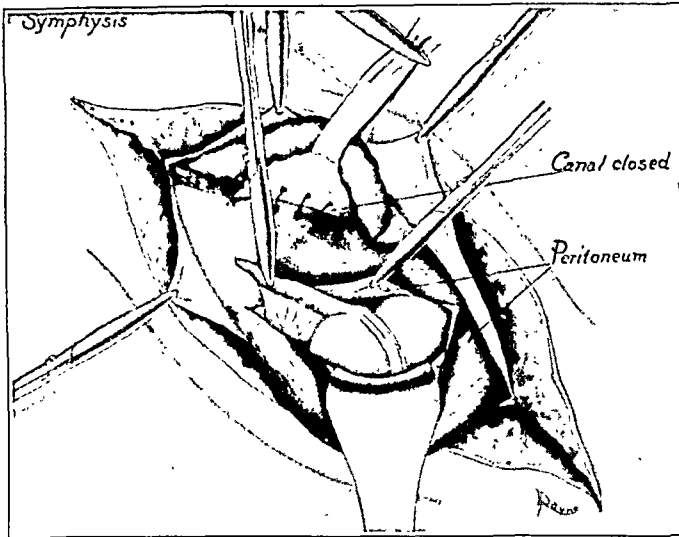


Fig. 23.—Operation for hernia, seen from the abdominal side. After the removal of the sac and closure of the canal, the appendix is delivered and about to be removed.

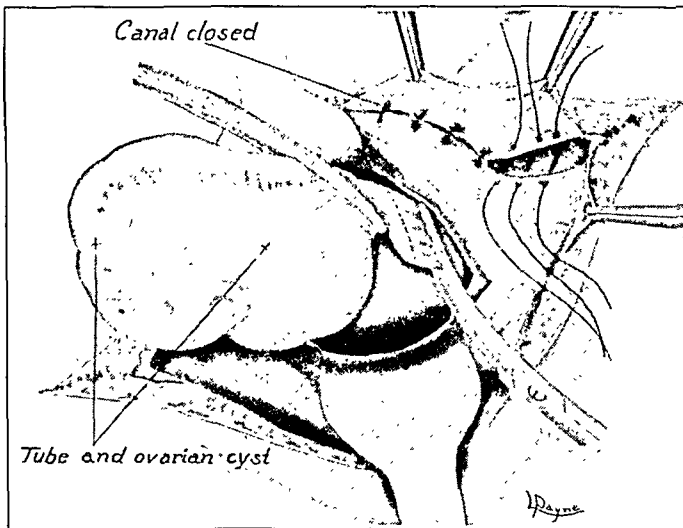


Fig. 24.—After removal of a hernia in a woman, the tubo-ovarian cyst is delivered into the wound, clamped and about to be removed.

percentage of patients were seen and examined at their homes by their doctors and by myself. In this way I have studied hundreds of patients after operation, and I have been able to find so few failures that I would not attempt to determine the percentage lest I myself be misled into a

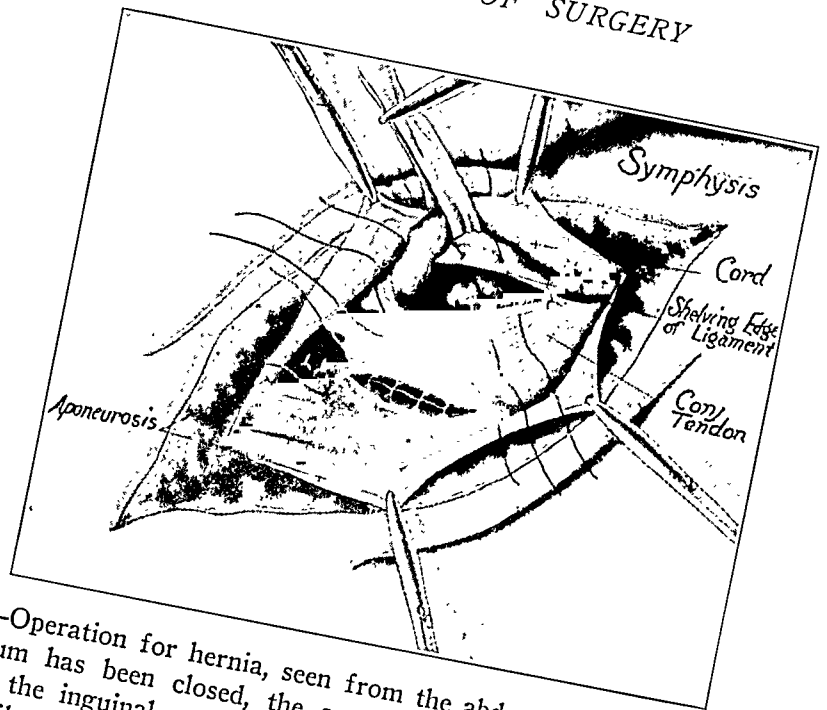


Fig. 25.—Operation for hernia, seen from the abdominal side. The incision in the peritoneum has been closed, the separated muscle fibers are being sutured together and the inguinal canal is being closed by sewing the conjoint tendon and arching fibers of the internal oblique muscle to the shelving edge of Poupart's ligament under the cord.

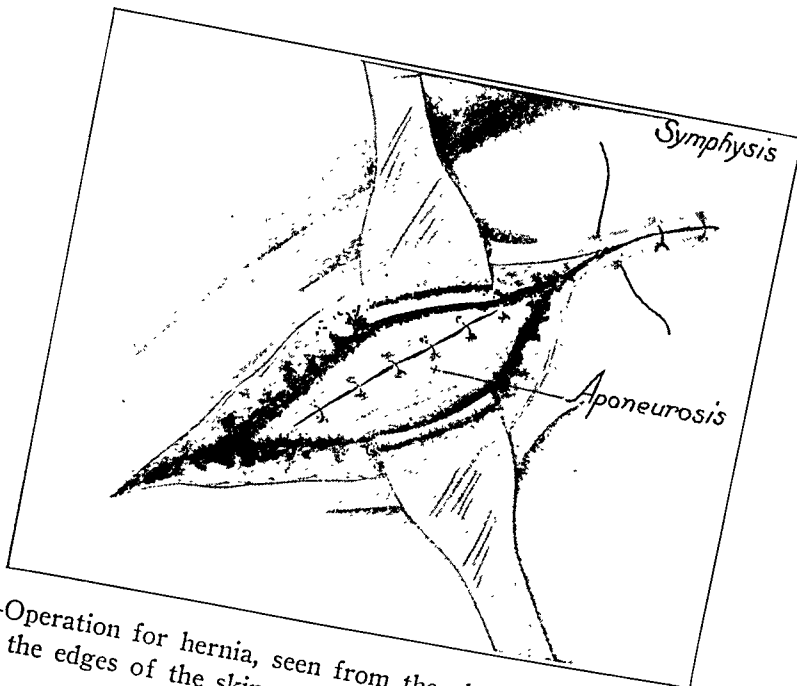


Fig. 26.—Operation for hernia, seen from the abdominal side. The aponeurosis is closed and the edges of the skin are being sutured.

false belief. Every one knows that grateful patients dislike very much to report failures. Ungrateful ones and those of hypercritical dispositions sometimes speak of unsuccessful results and present themselves with a bulge in some portion of the abdominal wall which on examination is found to be in no sense abnormal. I have been able to reexamine several hundreds of so-called difficult hernias of large size, and have seen a sufficient number of these put to the test of hard work, heavy lifting and other straining efforts, to lead me to the conclusion that this method of operating will permit the surgeon of average ability to be rewarded by a percentage of cures so much higher than that obtained by the better operative surgeons by the old method that the superiority of the abdominal approach admits of little debate.

The only failures that can occur in this method of operation would be those due to breaking of sutures, the result of postoperative coughing, or the opening of the wound with subsequent scar formation resulting from infection.

THE AERODYNAMICS OF BRONCHIAL OBSTRUCTION *

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It is well recognized that the intrapulmonary currents of air have an important bearing on bronchial obstruction. Obstruction from accumulation of secretions complicates bronchitis most frequently when the breathing is superficial. Both prevention and relief of obstruction may be promoted by the application of deep breathing exercises and of vigorous, well controlled coughing. Following the extensive investigations of Henderson and Haggard in the production of hyperpnea by the inhalation of carbon dioxide, the practice of administering this gas to patients after operation has become a routine measure in many surgical clinics. Nevertheless, the aerodynamics of bronchial obstruction is not understood in certain essential respects. It is not known, for instance, how deep breathing introduces air into a collapsed section of lung, the bronchi of which are filled with mucus; nor, under the same conditions, how cough evacuates the mucus. Conversely, the cause is not clear for the failure of deep breathing and coughing to obtain the results in many cases. Archibald¹ pointed out that inconstant and diverse effects of cough may be visualized plainly in man and in dogs during fluoroscopic examination of the bronchial tree with the use of radio-opaque oils. A column of such oil in a bronchus is usually thrown by a cough to the trachea, but at times the oil is thrown to the alveoli, or it is not displaced appreciably in either direction. The force of the impulse received by the oil is evidently governed by the vigor of the cough, but the direction of the impulse is not so determined. It is not known what determines the direction.

Another obscure subject in bronchial aerodynamics is that which relates to valvular action of masses obstructing the bronchi in the production of pulmonary atelectasis. Numerous cases are known² in which

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1. Archibald, E., and Brown, A.: *Am. Rev. Tuberc.* **16**:111, 1927.

2. Bergamini, H., and Shepard, L.: *Ann. Surg.* **86**:35, 1927. Lillenthal, H., quoted by Jackson, C.: *Mechanism of Physical Signs in Neoplastic and Other Diseases*, J. A. M. A. **95**:639 (Aug. 30) 1930. Hegner, C.: Personal communication to the authors. Heuer, G.: Personal communication to one of the authors.

a part of the lung collapsed with a rapidity that would appear to rule out absorption as the mode of removal of the air; and to explain the circumstance it has been suggested³ that the bronchus of the collapsed part was obstructed and the obstruction behaved as a valve permitting air to pass outward only. Each respiratory cycle then resulted in reducing by a fraction the volume of air in the lung distal to the obstruction, until atelectasis was complete. Most writers have discarded the theory,⁴ but they offer no satisfactory reasons for doing so. Coryllos and Birnbaum⁵ explained the rapid disappearance of air in these cases by their theories concerning absorption of alveolar gases. Of course, neither of these explanations accounts very well for the collapse in the instances in which careful search of the bronchial tree at autopsy failed to disclose the presence of secretions or other obstructing materials; but, in those in which obstruction was present, the simple mechanical theory of the valve cannot logically be discarded so summarily as it has been, especially since it is known to be a fact that bronchial obstructions have valvular actions at times. Jackson⁶ has seen the phenomena bronchoscopically in patients on numerous occasions. The obstruction, whether it was a foreign body, a ball of inspissated secretion or a pedunculated intrabronchial neoplasm, was observed to move in rhythm with respiration in relation to the orifice of a bronchus or to an abnormal isthmus in the bronchial lumen, closing the passage during inspiration and opening it again during expiration. Van Allen and Adams⁷ experimented with an artificial bronchial valve. A dog was anesthetized, and a cork perforated by a cannula was inserted into the right primary bronchus. A narrow rubber tube led from the cannula out of the trachea and extended to a glass of water in which its tip was submerged. After that, as long as the breathing was free and superficial, the water merely rose and fell a short distance in the tube with respiration and no air was lost from the tube; but when the outlet of the trachea was partly blocked during each expiration (in imitation of the action of the vocal cords during moaning, grunting and coughing) and the expirations became strained, the tube emitted a stream of bubbles at every breath and the obstructed part of the lung collapsed within a very few minutes. Van Allen and Adams preferred not to apply this to explain the collapse of the lung in clinical cases, thinking

3. Gairdner, W.: *Month. J. M. Sc.* **11**:122 and 230, 1850; **12**:440, 1851; **13**:2 and 238, 1851. Jackson C.: *Mechanism of Physical Signs in Neoplastic and Other Diseases of the Lung, with Special Reference to Atelectasis and Emphysema*, J. A. M. A. **95**:639 (Aug. 30) 1930.

4. Brunn, H., and Brill, S.: *Ann. Surg.* **92**:801, 1930.

5. Coryllos, P., and Birnbaum, G.: *Obstructive Massive Atelectasis of the Lung*, *Arch. Surg.* **16**:501 (Feb.) 1928.

6. Jackson (footnote 3, second reference).

7. Van Allen, C. M., and Adams, W.: *Surg., Gynec. & Obst.* **50**:385, 1930.

that the conditions of the experiment were different in one essential respect, at least, from those of clinical bronchial obstruction. In the former, the valve was directly faced on one side by the outer atmosphere, whereas, in the latter, the valve is faced on both sides by the bronchial atmosphere. They believed that an element of the same sort might be present in the bronchoscopic observations referred to, for there the bronchoscope led past the vocal cords and introduced the outer atmosphere directly and selectively to the outer face of the valve. Whether these differences were important in the matter of valvular action, and, if so, why they were, was not certainly known. An answer awaited a better understanding of bronchial aerodynamics.

During the course of some recent experimental work on problems pertaining to bronchial obstruction, a method was developed whereby the intrabronchial currents of air at the point of an obstruction could be observed directly and their forces measured. The method was an elaboration of that with a water valve, of Van Allen and Adams, but it obtained the essential physical circumstances of bronchial obstruction. Accordingly, the method was used in a series of experiments with the purpose of investigating systematically and defining the principles of the respiratory aerodynamics in bronchial obstruction. The varieties of bronchial obstruction that have been noted in man and the forms of respiration that accompany them were imitated in animals for the study. These experiments and their results form the subject of the present paper.

It will be necessary, first of all, to describe briefly a newly discovered⁸ function of the lungs, termed collateral respiration,⁸ which enters very significantly into bronchial aerodynamics. This function depends on the fact that the lobular divisions of the bronchial tree of any one pulmonary lobe are interconnected abundantly at the periphery, rather than being independent as has been generally supposed. The interlobular septums of the lung are incomplete, and the alveoli at the planes of fusion of the lobules communicate with each other by minute passages (probably the alveolar pores of Kohn), and perhaps, too, by diffusion through the alveolar walls. The communication is brought spontaneously into operation when the bronchus supplying one lobule or group of lobules becomes obstructed, for then the obstructed part breathes by way of the collateral connections with the parts of the lobe remaining free. Thus, with inspiration, air that passes to the periphery of the free lobules enters collaterally into and inflates the obstructed lobules; and, with

8. Van Allen, C. M.; Lindskog, G. E., and Richter, H. G.: *Yale J. Biol. & Med.* **2**:297, 1930. Van Allen, C. M., and Lindskog, G. E.: *Obstructive Pulmonary Atelectasis*, *Arch. Surg.* **21**:1195 (Dec.) 1930; *Collateral Respiration in the Lung*, *Surg., Gynec. & Obst.* **53**:16, 1931. Van Allen, C. M.; Lindskog, G. E., and Richter, H. G.: *J. Clin. Investigation* **10**:559 (Aug.) 1931.

expiration, air to be discharged from the obstructed lobules escapes by the same path into the free lobules and passes out with the expired air of those parts. Respiration may continue in this manner and maintain the inflation of the obstructed lobules as long as obstruction lasts. Examples are known in man,⁹ as well as in experimental animals,¹⁰ in which large sections of lobes remained fully air-containing indefinitely after bronchial obstruction. Collateral respiration is interrupted whenever the patency of the alveoli and bronchioles at the planes of fusion of the obstructed and free parts of the lung is lost, as may occur from accumulation of inflammatory exudates and secretions or from insufficient respiratory expansion. There is no provision (in man and dog) for collateral respiration between the lobes of the lung. The interlobar fissures and septums are complete and prevent it. When the bronchus supplying one or more entire lobes is obstructed, the airways of those parts are necessarily isolated from the airways of the rest of the lung and from the outer atmosphere. Broadly speaking, collateral respiration serves the bronchial system in the same economic capacity as does collateral circulation the vascular system.

EXPERIMENTAL METHOD

The experiments were acute. For each one a dog was anesthetized and tracheotomized, and two long cannulas were introduced through the trachea into one bronchus. One cannula was entered a little farther than the other, and its tip was expanded in the bronchus to produce an air-tight fit, while the internal end of the other was laid quite freely in the lumen. The external ends were connected by interposing a valve between them. This produced an extension of the bronchial passage to the outside and back along a U-shaped course (fig. 1). The valve served to obstruct the air currents respired through the bronchial passage, and it was so constructed as to exhibit nicely to open view the behavior of the currents at the obstruction (valve to be described). Two manometers were attached to the passage, one distal to the valve and the other proximal to it. A third cannula was introduced through the wall of the chest into the pleural cavity at a point immediately over the obstructed lobe. It was attached to a third manometer.

The circumstances of the experiments were caused to vary in certain respects. On different occasions, two positions and three types of obstruction were formed and two types of breathing were induced. Thus, there was lobular obstruction (figs. 1 and 2 *A, B* and *C*), or that with the cannula fixed in the stem bronchus of the right lower lobe at a point just distal to the first branch; and lobar obstruction (fig. 1, *K*, and fig. 2, *D, E* and *F*), or that with the cannula fixed in the right primary bronchus at a point just proximal to the branches supplying the lower and accessory lobes. Also, there were total obstruction (fig. 2, *A* and *D*), or that with the cannular passage closed continuously on both sides of the valve; simple inspiratory obstruction (fig. 2, *B* and *E*), or that with the valve arranged

9. Van Allen, C. M., and Ch'in, K.: Work in progress.

10. Adams, W.: Proc. Soc. Exper. Biol. & Med. 27:982, 1930. Brill, S., and Brown, A., quoted by Jackson (footnote 3, second reference). Van Allen, Lindskog and Richter (footnote 8, first reference).

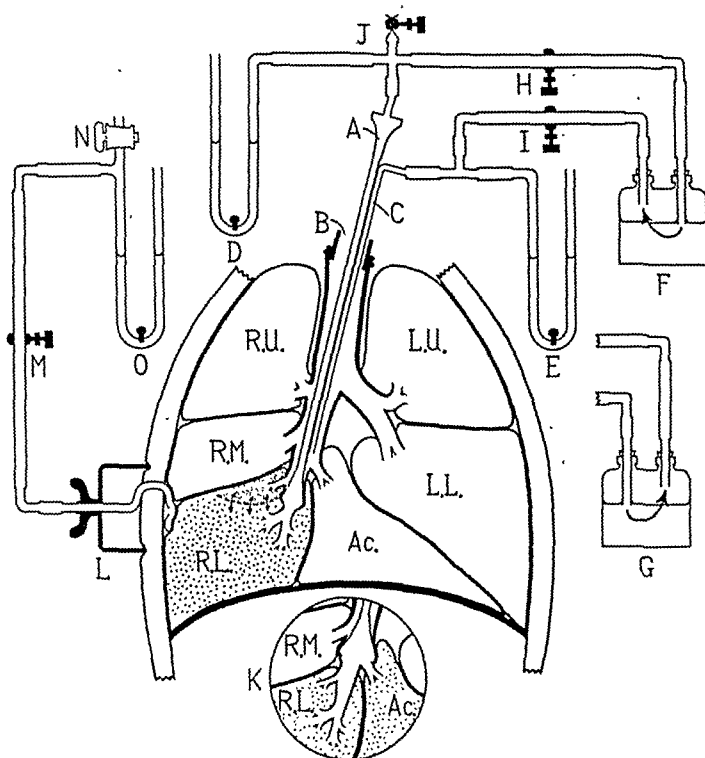


Fig. 1.—Diagram of a frontal section of a dog's chest walls and lung and of the apparatus arranged in place. *A* indicates the dilatable bronchial cannula, fixed in the stem bronchus of the right lower lobe (*R.L.*) at a point just distal to the first branch, as used to produce lobular obstruction; the arrows below, paths of collateral respiration between the obstructed part (lightly dotted) and the free part (heavily dotted) of the lobe; *K*, insert showing point of fixation of the dilatable cannula in the right primary bronchus just proximal to the bronchi of the right lower (*R.L.*) and accessory (*Ac.*) lobes, as used to produce lobar obstruction; *B*, tracheotomy opening; *C*, nondilatable cannula, terminating freely in the right primary bronchus; *D* and *E*, manometers connected to the cannulas; *F*, water valve connecting the cannulas, as used for simple inspiratory obstruction; *G*, insert showing arrangement of water valve for simple expiratory obstruction; *H* and *I*, pinch-cocks to be closed for total obstruction; *J*, pinch-cock to be opened for relief of obstruction; *L*, pleural cannula; *M* and *N*, cocks; *O*, pleural manometer. In some experiments manometers, *D* and *E*, were replaced by tambours with writing arms and a kymograph.

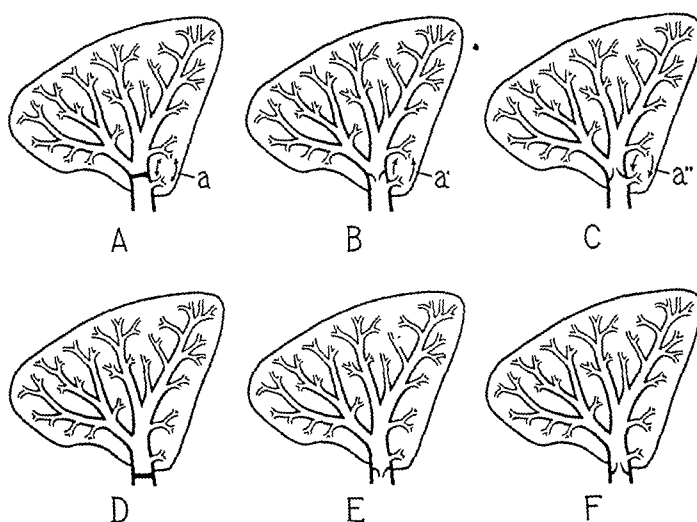


Fig. 2.—Diagrams of the bronchial tree of the dog's right lower pulmonary lobe, showing in principle the conditions of obstruction that were studied. *A*, *B* and *C* indicate lobular obstruction; *a*, *a'* and *a''*, paths and directions of collateral respiration; *D*, *E* and *F*, lobar obstruction (the second lobe, which was included, is not shown); *A* and *D*, total obstruction; *B* and *E*, simple inspiratory obstruction; *C* and *F*, simple expiratory obstruction.

so as to close the passage only at inspiration, and simple expiratory obstruction (fig. 2, *C* and *F*), or that with the valve arranged so as to close the passage only at expiration. And, finally, free breathing, or that with the trachea kept open about the cannulas continuously for respiration of the nonobstructed parts of the lung, and coughing breathing, or that in which the effects of cough were imitated from time to time with certain manipulations at the tracheal outlet were induced (see under technic). These experimental variables were used in twelve different combinations, and each combination was investigated on from two to six occasions during the course of eleven experiments.¹¹

Each experiment was divided into parts, the parts dealing with different combinations of the experimental variables. To start each part, the obstruction was relieved for a few minutes (fig. 1, pinch-cock *J* opened), the apparatus was adjusted to provide the desired circumstances, and then the obstruction was suddenly instituted (fig. 1, pinch-cock *J* closed) at the height of either inspiration or expiration. Observations were begun immediately thereafter. These included reading the three manometers,¹² both at inspiration and at expiration, and watching the behavior of the air at the valve. They were made simultaneously by several observers and were repeated as often and as long as necessary to demonstrate the changes that occurred. One experiment differed from the rest, in that the dog was dead and respiratory excursions of the walls of the chest were made artificially.

The results of the experiments are presented in the form of outlines and charts. Duplicate data are omitted as far as possible, but reference is made only to those features of the reactions that were repeatedly seen in the same forms and were believed to be quite characteristic. The varieties of reaction that occurred in the different combinations of experimental variables are illustrated.

APPARATUS

Dilatable Bronchial Cannula (fig. 3).—The mechanism of this instrument has been explained elsewhere.¹³ The cannula was 40 cm. in length and 0.25 cm. in internal diameter. The end for introduction could be dilated forcefully in situ in the bronchus by revolving a screw at the other end, and it then presented a narrow ring of metal and rubber to the inner surface of the bronchus for attachment. Dilatation could be extended sufficiently to stretch tightly a dog's bronchus of any size. The attachment was secure against accidental dislodgment, and it was selective and thoroughly air-tight.

Nondilatable Bronchial Cannula (fig. 1, *C*).—This instrument was a simple straight metal tube, of the same internal diameter as the dilatable cannula and a little shorter.

11. These were the last of a series of thirty-two experiments. The earlier ones were occupied in developing the various aspects of the problem and in standardizing the technic. The data obtained from the earlier experiments helped greatly to confirm the conclusions that have been reached, but they will not be referred to directly in this paper because of the lack of uniformity in experimental method that existed.

12. The manometers were read directly. It was necessary to obtain absolute pressures, and the use of floats and writing arms for automatic recording was undesirable because of the inaccuracy produced by friction.

13. Van Allen, C. M.: Yale J. Biol. & Med. 2:297, 1930.

*Pleural Cannula*¹⁴ (fig. 1, L).—This cannula consisted of a metal tube bent approximately to the shape of a question mark, together with a metal housing and a winged nut. The hooked portion of the cannula, which was meant to lie in the wall of the chest and pleural cavity, had a closed rounded end and a fenestrum on the concave aspect near the end. The fenestrum was for communication with the pleural cavity. The straight portion carried the connection with the manometer, also the housing and nut. The latter served to hold the cannula in place on the chest. A pinch-cock was situated between the cannula and manometer, to be closed during introduction of the cannula (forcing of the hooked portion bluntly through the soft tissues of the wall of the chest) and during adjustment of the manometer to atmospheric pressure. The arrangements thus permitted an entirely "closed" operation of the instrument.

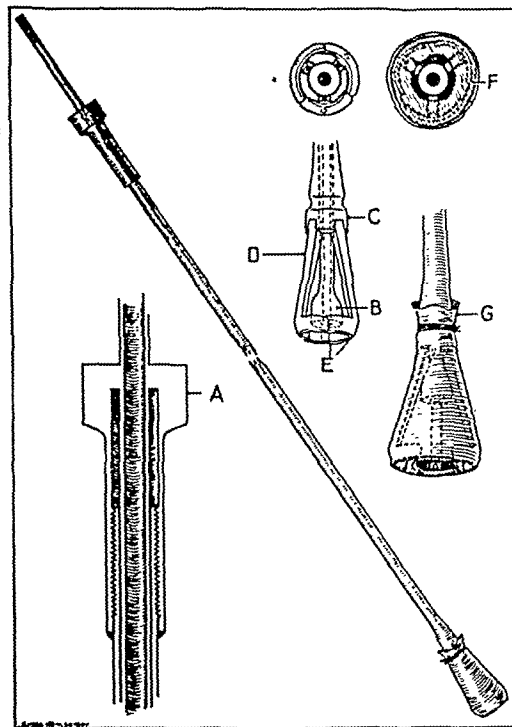


Fig. 3.—Plan of the dilatable bronchial cannula. In the center is shown a cannula ready for use; above, detail of the dilatable end, when dilated and when collapsed. B, C, D and E indicate parts of the dilating mechanism; F and G, rubber cap. Below is shown the detail of the reverse end. A indicates a screw for producing dilatation.

Valve (fig. 1, F and G).—This was a glass, double-necked bottle partly filled with water, which was fitted with two corks each pierced by a glass tube. One tube terminated above the water and the other extended from 1 to 2 mm. under it. The tubes carried the connections with the bronchial cannulas. Thus, the arrangement was such as to allow air to flow through the bottle from one cannula to the other only in the direction from the submerged tube to the elevated one, and to betray delicately by changes in the level of the water in the submerged tube the movements of air in either direction.

14. Adapted from a cannula used in the laboratory of Dr. I. S. Ravdin.

Manometers.—These instruments differed from the common U-shaped manometer in one important respect. At the bend of the U was a set-screw by which the lumen could be narrowed to any degree. This was used to dampen the after-swing of the column of fluid and to increase the accuracy of the readings at times when the rate of respiration was too rapid and the period of swing too short to allow the column to come to rest for reading without such dampening. Water was the medium, it being best adapted to register the small pressures encountered. Tambours were employed in place of manometers in a few experiments, in order to secure kymographic records. Particular care was taken to equalize the tension of the tambours and to make the tracings directly comparable.

SPECIAL TECHNIC

Preparation of the Dog.—A preliminary hypodermic injection of morphine, from 0.030 to 0.045 Gm., and atropine, from 0.002 to 0.004 Gm., was given. The dog was anesthetized with ether and fastened in the dorsal recumbent position. The trachea was exposed by midline incision, and it was completely severed from the larynx. The tracheal opening was fitted with a glass sleeve, tied in place, to hold it wide for instrumentation and to control oozing of blood. The anesthesia was then carried on by directing a stream of ether vapor and air at the tracheal outlet.

Management of Breathing.—Institution of free breathing required no additional adjustment, for there was ample space in the trachea beside the cannulas for passage of the air respired by the nonobstructed parts of the lung. The respirations were regulated and kept at moderate depth and steady rate, as nearly as possible, by adjusting the composition of the ether-air mixture. In preparation for experiments requiring the use of cough, the dog was given a smaller dose of morphine than otherwise and was kept under a very light anesthesia with ether. This caused deep and somewhat irregular respiration. When a cough was wanted, the breathing was watched carefully and at the height of an unusually full inspiration the outlet of the trachea was occluded completely with the finger, the occlusion was maintained during from one third to one half of expiration, and then the outlet was suddenly released. This maneuver produced momentary back pressure in the lower respiratory passages and explosive discharge of the imprisoned air. The dog usually reacted to the transient tracheal block with forceful expiratory effort, and, although the force of the act was less than that of the average natural cough, the essential effects of cough seemed to be represented. The act was always repeated several times to permit accurate observations of the effects.

Autopsy.—The apparatus was left in place at the termination of the experiment, the dog was killed by intravenous injection of ether, and autopsy was performed. The degree of inflation of the obstructed part of the lung was noted, and pathologic lesions were searched for. The position of the dilatable cannula was checked, and vigorous tests were made to determine the degree of air-tightness at the attachment.

RESULTS

FREE RESPIRATION

A. Obstruction: Lobar and Total (Fig. 2, D).—Begun at Height of Expiration (Observed Ten Minutes): Figure 4, *a*, shows that at first the distal pressure (intrabronchial pressure distal to obstruction; recorded by manometer, fig. 1, *D*) oscillated regularly with respiration from 0.4

to -2.8 cm. of water; the proximal pressure (intra-bronchial pressure proximal to obstruction; recorded by manometer, fig. 1, *E*) oscillated similarly from 0.2 to -0.2 cm.; the intrapleural pressure oscillated similarly from -5.4 to -8.8 cm. There was no important change. The obstruction was released.

Observation Begun at Height of Inspiration (Observed Thirty-Seven Minutes): It is seen in figure 4, *b*, that at first the distal pressure oscillated from 1.6 to -2.4 cm. of water. It fell gradually to a zone from 0.4 to -4 cm. after twenty minutes, and then it changed no more. The other pressures were essentially the same as in part *a*.

B. Obstruction: Lobar and Simple Inspiratory (Fig. 2, *E*).—Begun at Height of Expiration (Observed Twenty-Six Minutes): In figure 5

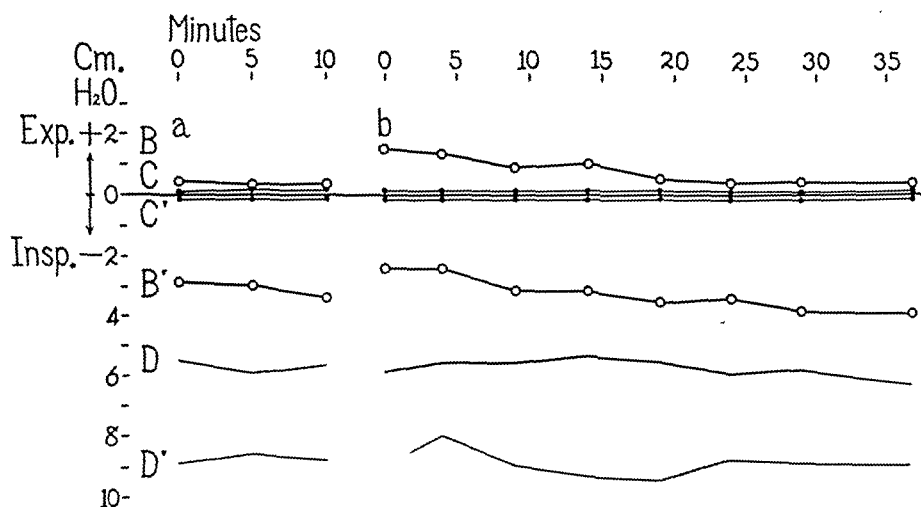


Fig. 4.—Total, lobar obstruction (see plan, fig. 2, *D*). 0 cm. H_2O indicates the level of atmospheric pressure; *B* and *B'*, curves representing the expiratory and inspiratory limits, respectively, of the range of oscillation of the intra-bronchial pressure distal to the obstruction; *C* and *C'*, the same type of curves for the intra-bronchial pressure proximal to the obstruction; *D* and *D'*, the same type of curves for the intrapleural pressure; *a*, period with obstruction and observations begun at the height of an expiration (no tidal air in the obstructed part of the lung); *b*, period with obstruction and observations begun at the height of an inspiration (tidal air included in the part).

it is seen that at first the distal pressure oscillated from 1.8 to -5.6 cm. of water; the proximal pressure, from 0.2 to -0.2 cm.; the intrapleural pressure, from -4.6 to -11 cm. With the first expiration, air bubbled heavily at the valve (leaving the lung); with the second, slightly less bubbling occurred; with the third, still less; with the fourth, one bubble passed; then no more passed, and the water in the submerged tube merely rose and fell a few centimeters with respiration. During the first four breaths, the level of the distal pressure at expiration fell rapidly to

0.3 cm. of water, and then it remained at that level. Other pressures showed no important changes throughout.

C. Obstruction: Lobar and Simple Expiratory (Fig. 2, *F*).—Begun at Height of Expiration (Observed Sixty Minutes): Figure 6 shows that at first the distal pressure oscillated from 0.4 to —6.6 cm. of water; the proximal pressure, from 0.2 to —0.2 cm., and the intrapleural pressure, from —4.3 to —11 cm. With every inspiration for twelve minutes air bubbled heavily at the valve (entering the lung), and the distal pressure rose steadily to a zone from 5.6 to —2.6 cm. of water. Bubbling was then slightly less for twenty minutes, and the distal pressure rose more gradually to a zone from 6 to —1.2 cm. After that, bubbling was still less and occurred only at every third or fourth inspiration. There was

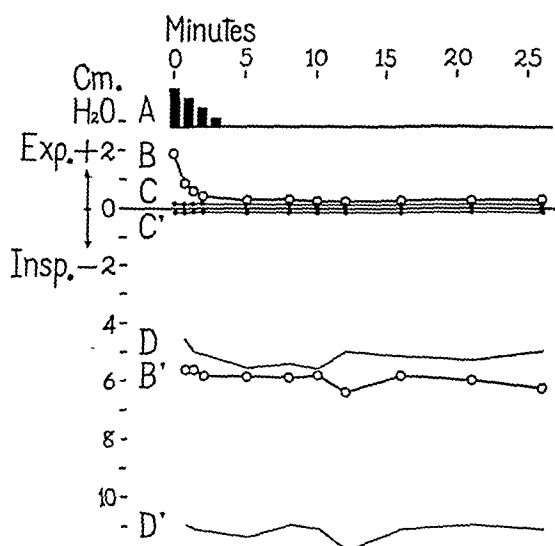


Fig. 5.—Simple inspiratory, lobar obstruction (see plan, fig. 2, *E*). *A* indicates columns representing relatively the amounts of air expelled through the valve at each expiration. Obstruction and observations were begun at the height of an inspiration (tidal air in the obstructed part). The designations are otherwise the same as in figure 4.

no further important change in pressure. The other pressures showed no important changes throughout. The dog was killed. The distal pressure rose immediately to 9.2 cm. of water; the intrapleural pressure to 2.6 cm. Autopsy showed that the obstructed lobes were markedly emphysematous and that the mediastinum was displaced distinctly to the left.

D. Obstruction: Lobular and Total (Fig. 2, *A*).—Begun at Height of Expiration (Observed Ten Minutes): In figure 7, *a*, it is seen that at first the distal pressure oscillated from 1.6 to —1.6 cm. of water, and the proximal pressure, from 0.2 to —0.2 cm. There was no important change. The obstruction was released.

Obstruction Begun at Height of Inspiration (Observed Thirty-Five Minutes): Figure 7, *b*, shows that the pressures were practically the same as in part *a* and remained so throughout.

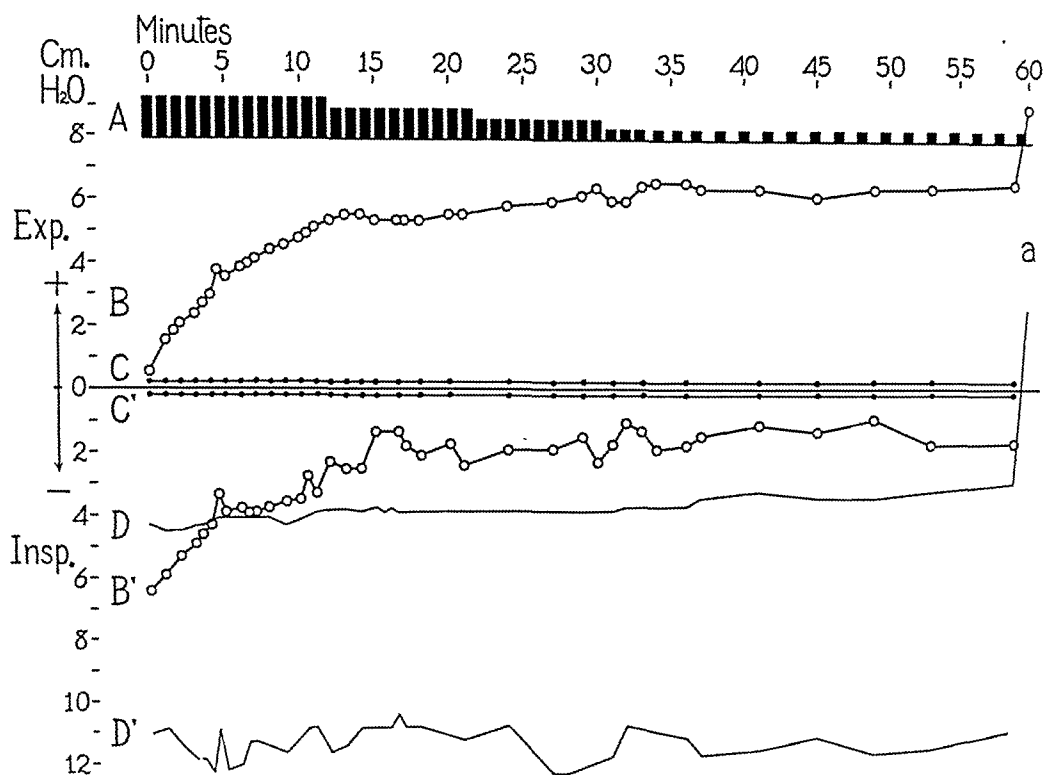


Fig. 6.—Simple expiratory, lobar obstruction (see plan, fig. 2, *F*). *A* indicates columns representing relatively the amounts of air received through the valve at each inspiration. Obstruction and observations were begun at the height of an expiration (no tidal air in the obstructed part). The designations are otherwise the same as in figure 4. The dog was killed at sixty minutes. The readings made immediately after death are indicated by *a*.

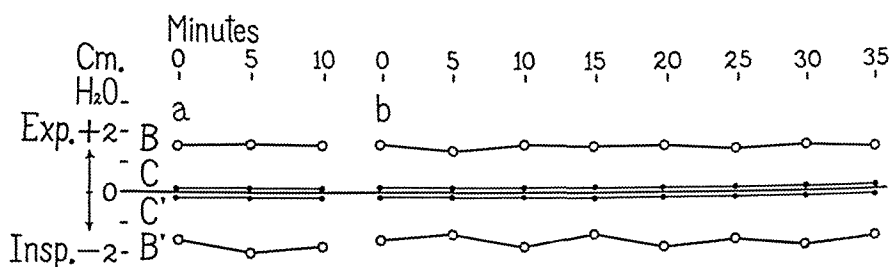


Fig. 7.—Total, lobular obstruction (see plan, fig. 2, *A*). The designations are the same as in figure 4, omitting intrapleural pressures.

E. Obstruction: Lobular and Simple Inspiratory (Fig. 2, *B*).—*Begun at Height of Expiration* (Observed Thirty-five Minutes): It is seen in figure 8 that at first the distal pressure oscillated from 1.2 to —5 cm. of water; the proximal pressure, from 0.3 to —0.3 cm. There was no important change. Air bubbled heavily at the valve (leaving

the lung) with each expiration throughout. The dog was killed. Autopsy showed that the obstructed part of the lobe was normally inflated.

F. Obstruction: Lobular and Simple Expiratory (Fig. 2, C).—Begun at Height of Expiration (Observed Thirty-Five Minutes): Figure 9 shows that at first the distal pressure oscillated from 3.2 to -2 cm. of water; the proximal pressure, from 0.2 to -0.2 cm. There was no important change. Air-bubbled heavily at the valve (entering

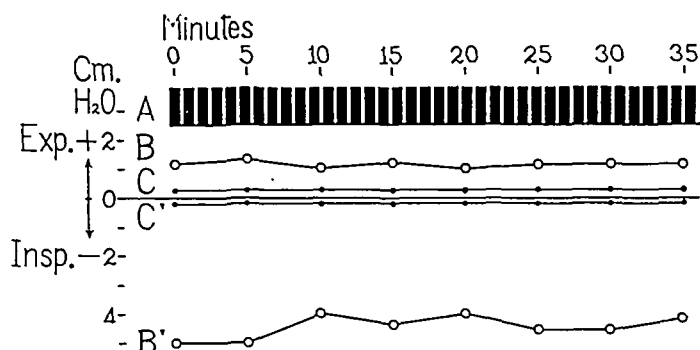


Fig. 8.—Simple inspiratory, lobular obstruction (see plan, fig. 2, B). Obstruction and observations were begun at the height of an expiration (no tidal air in the obstructed part). Intrapleural pressures are omitted. The designations are otherwise the same as in figure 5.

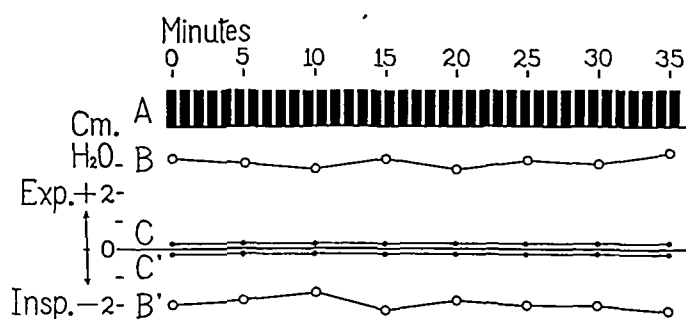


Fig. 9.—Simple expiratory, lobular obstruction (see plan, fig. 2, C). Obstruction and observations were begun at the height of an expiration (no tidal air in the obstructed part). Intrapleural pressures are omitted. The designations are otherwise the same as in figure 6.

the lung) with each inspiration throughout. The dog was killed. Autopsy showed that the obstructed part of the lobe was normally inflated.

COUGHING

A. Obstruction: Lobar and Total (Fig. 2, D).—Begun After Death; Tracheal Outlet Closed Completely About Bronchial Cannulas: From figure 10, *a*, it is seen that the distal pressure was 0 cm. of water; the proximal pressure, 0 cm.; the intrapleural pressure, -4.6

cm. The walls of the chest were squeezed together manually with moderate force. The distal pressure was 6 cm. of water; the proximal pressure 6 cm.; the intrapleural pressure, 1.3 cm. The walls of the chest were then released. The pressures returned approximately to the original values. The tracheal outlet was opened.

Five Cubic Centimeters of Air Injected into Dilatable Cannula (Into Obstructed Lobes); Tracheal Outlet Closed: From figure 10, *b*, it is seen that the distal pressure was 2 cm. of water; the proximal pressure, 0 cm.; the intrapleural pressure, —4.5 cm. The walls of the chest were squeezed together. The distal pressure was 10 cm. of water; the proximal pressure, 7.6 cm.; the intrapleural pressure, 5 cm. The walls of the chest were then released. The pressures returned approximately

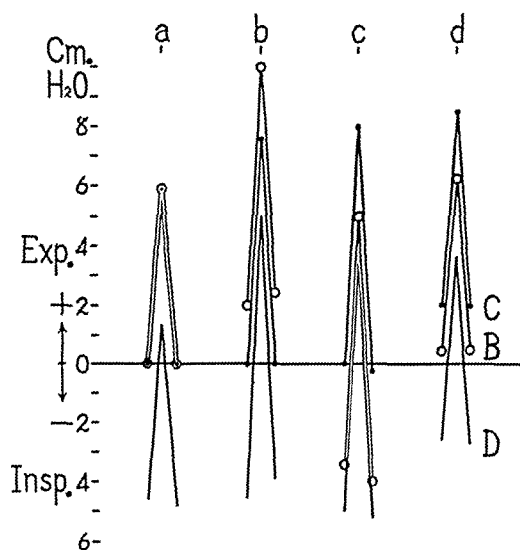


Fig. 10.—Total, lobar obstruction (see plan, fig. 2, *D*), instituted immediately after death. *B* indicates intrabronchial pressure distal to obstruction; *C*, this pressure proximal to obstruction; *D*, intrapleural pressure; *a*, period with obstruction and observations begun with the lung inflated as at death; *b*, period, begun after tidal air had been injected into the obstructed part of the lung; *c*, period, begun after tidal air and a part of residual air had been aspirated from the obstructed part; *d*, period, begun with the obstructed part inflated as at death and after tidal air had been injected into the free part of the lung. In each period there were three readings, the first without other manipulation, the second with the chest squeezed, and the third, again, without that manipulation.

to the original values. Added air was removed from the dilatable cannula. The tracheal outlet was opened.

Five Cubic Centimeters of Air Aspirated from Dilatable Cannula (From Obstructed Lobes): Figure 10, *c*, shows that the distal pressure was —3.4 cm. of water; the proximal pressure, 0 cm.; the intrapleural pressure, —5 cm. The walls of the chest were squeezed together. The distal pressure was, 5 cm. of water; the proximal pressure, 8 cm.;

the intrapleural pressure, 3.4 cm. The walls of the chest were then released. The pressures returned approximately to the original values. Subtracted air was returned into the dilatable cannula. The tracheal outlet was opened.

Tracheal Outlet Closed; Fifteen Cubic Centimeters of Air Injected into Nondilatable Cannula (Into Nonobstructed Lobes): From figure 10, *d*, it is seen that the distal pressure was 0.4 cm. of water; the proximal pressure, 2 cm.; the intrapleural pressure, 2.6 cm. The walls of the chest were squeezed together. The distal pressure was 6.2 cm. of water; the proximal pressure, 8.5 cm.; the intrapleural pressure, 3.6 cm. The walls of the chest were released. The pressures returned approximately to the original values.

*B. Obstruction: Lobar and Total (Fig. 2, D).—*Begun at Height of Expiration; Living Dog; Tambours Replacing Bronchial Manometers (Kymographic Tracings Observed): It is seen in figure 11,

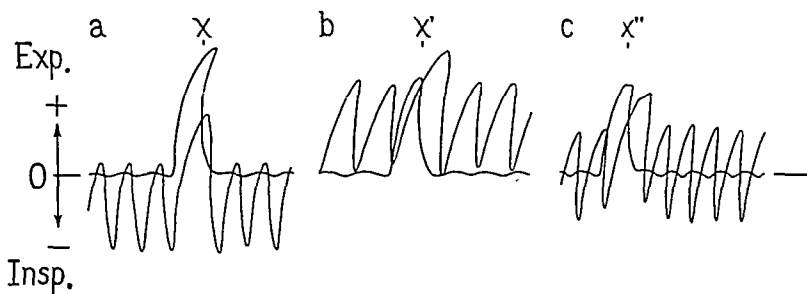


Fig. 11.—Kymographic tracings in total, lobar obstruction. *O* indicates the level of atmospheric pressure. Curves that oscillate widely and constantly represent the intrabronchial pressure distal to the obstruction. Other curves represent the intrabronchial pressure proximal to the obstruction. Intrapleural pressure is omitted. *a* indicates the period with obstruction begun at the height of an expiration (no tidal air in the obstructed part); *b*, period with obstruction begun at the height of an inspiration (tidal air included); *c*, period with obstruction begun at the middle of an expiration (one half of tidal air included); *x*, *x'* and *x''*, single coughs.

a, that at first the distal pressure oscillated regularly with respiration, the expiratory level lying slightly above atmospheric pressure and the inspiratory level lying markedly below that pressure; the proximal pressure oscillated similarly but very slightly at atmospheric pressure. One cough was produced at the fourth breath. Both pressures rose together sharply to much higher levels than before, the proximal pressure higher than the distal pressure, and they fell immediately to the original levels and oscillated as before. The obstruction was released.

Obstruction Begun at Height of Inspiration: Figure 11, *b*, shows that at first the distal pressure oscillated with respiration, the expiratory level lying markedly above atmospheric pressure and the inspiratory level lying at that pressure; proximal pressure oscillated very slightly at

atmospheric pressure. One cough was produced at the third breath. Both pressures rose together sharply to higher levels than before, the distal pressure higher than the proximal pressure, and they fell immediately to the original levels and oscillated as before. The obstruction was released.

Obstruction Begun at Midpoint Between Heights of Inspiration and Expiration: It is seen from figure 11, c, that at first the distal pressure oscillated, the expiratory and inspiratory levels lying equidistant from the atmospheric pressure; the proximal pressure, very slightly at atmospheric pressure. One cough was produced at the third breath. Both pressures rose together sharply to higher levels than before, about equal in elevation, and they fell immediately to the original levels and oscillated as before.

Circumstances Unaltered; Cough Produced at Every Breath, Kymograph Moving Rapidly: Figure 12 shows that at the beginning of the first cough (*a*, height of inspiration) the distal pressure was at a

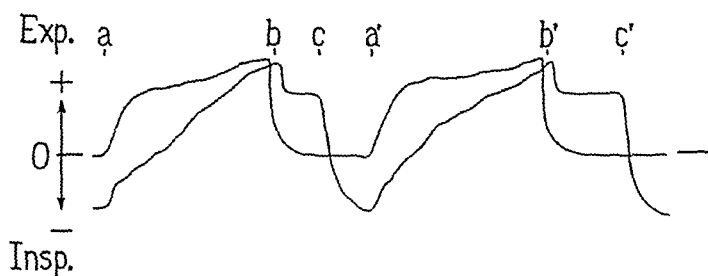


Fig. 12.—Kymographic tracings in total, lobar obstruction, obtained during two successive coughs and with the kymograph moving rapidly. *O* indicates the level of the atmospheric pressure. The curve that begins lower represents the intra-bronchial pressure distal to the obstruction. The other curve represents the intra-bronchial pressure proximal to the obstruction. *a* to *c* indicates the period of the first cough; *a'* to *c'*, period of the second cough; *a* to *b* and *a'* to *b'*, first phase of cough (tracheal outlet closed); *b* to *c* and *b'* to *c'*, second phase of cough (tracheal outlet open); *c* to *a'*, inspiration between the coughs.

moderate distance below atmospheric pressure; the proximal pressure, at atmospheric pressure. At this time the tracheal outlet was closed for two-thirds the expiration (*a* to *b*, first phase of cough), and both pressures rose rapidly to levels markedly above atmospheric pressure, about equal in elevation. The tracheal outlet was opened for the remainder of expiration (*b* to *c*, second phase of cough), and both pressures fell, the distal pressure slightly and the proximal pressure markedly and completely to its original level. At the end of the first cough (*c*, height of expiration) the distal pressure began to fall, and the fall continued throughout the following inspiration (*c* to *a'*) until it reached the original level. The second cough (*a'* to *c'*) showed the same type of behavior of the pressure.

C. Obstruction: Lobar and Simple Inspiratory (Fig. 2, E).— Begun at Height of Expiration (Observed Twenty-five Minutes): It is seen from figure 13 that at first the distal pressure at expiration was 0.2 cm. of water; the proximal pressure was 0.1 cm. (Only these pressures are important here.) There was no change for five minutes. No bubbling occurred at the valve. One cough was produced (*a*). The distal pressure rose sharply to 3 cm. of water; the proximal pressure, to 6 cm. There was a very slight bubbling of air (leaving the lung). The distal pressure fell immediately to 0.1 cm. of water; the proximal pressure to 0.1 cm. There was no change for two min-

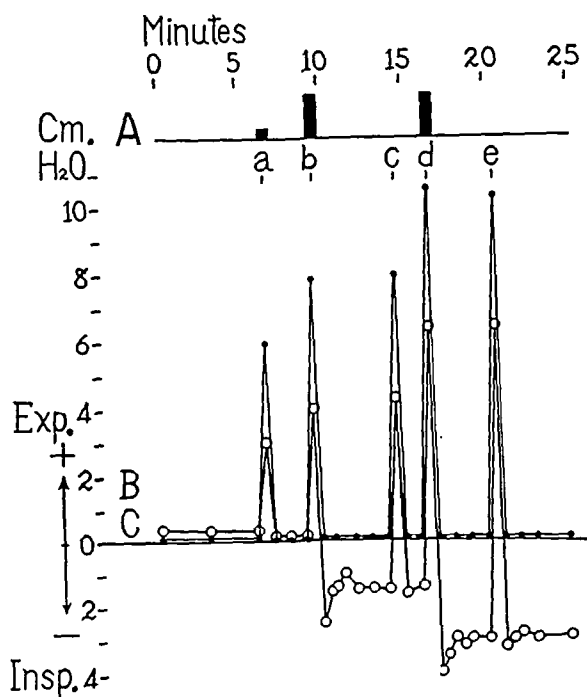


Fig. 13.—Simple inspiratory, lobar obstruction (see plan, fig. 2, E). 0 cm. H_2O indicates the level of atmospheric pressure; *A*, columns representing approximately the amounts of air expelled through the valve at each expiration; *B*, curve representing the expiratory limit of the range of oscillation of the intrabronchial pressure distal to the obstruction; *C*, the same type of curve for the intrabronchial pressure proximal to the obstruction; *a*, *b*, *c*, *d* and *e*, single coughs of various intensities.

utes and no bubbling. One harder cough was produced (*b*). The distal pressure rose to 4 cm. of water; the proximal pressure to 7.8 cm. Air bubbled heavily. The distal pressure fell to -2.4 cm. of water; the proximal pressure to 0.1 cm. The distal pressure then rose gradually to -1.2 cm. and remained stationary for two minutes. There was no bubbling. One cough was produced (*c*), equal in force to the last. The distal pressure rose to 4.3 cm. of water; the proximal pressure, to 8 cm. There was no bubbling. The pressures

fell to previous levels. One harder cough was produced (*d*). . The distal pressure rose to 6.4 cm. of water; the proximal pressure, to 10.6 cm. Air bubbled heavily. The distal pressure fell to —4 cm. of water, the proximal pressure, to 0.1 cm. The distal pressure rose gradually to —3 cm. in three minutes. There was no bubbling. One cough was produced (*e*), equal in force to the last. The distal pressure rose to 6.6 cm. of water; the proximal pressure, to 10.6 cm. There was no bubbling. The pressures fell to previous levels. (Further coughs, maximum in force and equal to the last two, caused no bubbling and no further depression of the distal pressure.)

D. Obstruction: Lobar and Simple Expiratory (Fig. 2, *F*).— Begun at Height of Expiration (Observed Seventy Minutes): It is seen from figure 14 that at first the distal pressure at expiration was

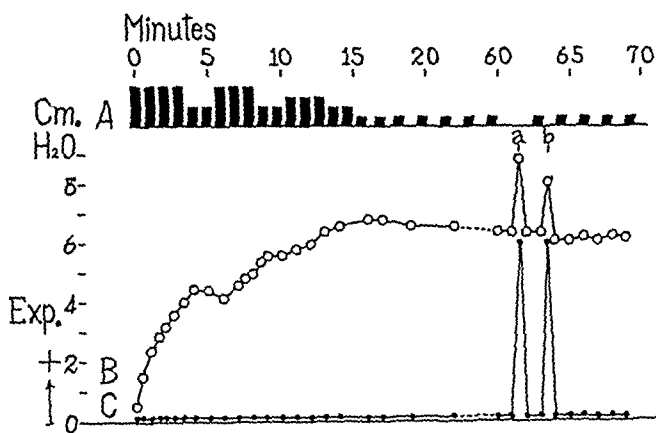


Fig. 14.—Simple expiratory, lobar obstruction (see plan, fig. 2, *F*). *A* indicates the columns representing approximately the amounts of air received through the valve at each inspiration; *a* and *b*, single coughs of different intensities. The designations are otherwise the same as in figure 13.

0.4 cm. of water; the proximal pressure, 0.1 cm. (Only these pressures are important here.) With every inspiration for four minutes air bubbled heavily at the valve (entering the lung), and the distal pressure rose steadily to 4.4 cm. Bubbling was then slightly less for ten minutes, and the distal pressure rose more gradually to 6.8 cm. After that, bubbling was still less and occurred only at every third or fourth inspiration, and the pressure showed no important change, in sixty minutes. The proximal pressure showed no change throughout. One cough was produced (*a*). The distal pressure rose sharply to 9 cm. of water; the proximal pressure, to 6 cm. There was no bubbling. The pressures fell immediately to the previous levels. Another cough was produced (*b*), with the same effects. The conditions continued as they were before coughing.

E. Obstruction: Lobular and Total (Fig. 2, *A*).—Begun at Height of Expiration (Observed Twenty-five Minutes): It is seen in figure 15 that at first the distal pressure at expiration was 1.6 cm. of water; the proximal pressure, 0.1 cm. (Only these pressures are important here.) There was no important change for eighteen minutes. One cough was produced (*a*). The distal pressure rose sharply to 5.8 cm. of water; the proximal pressure, to 7 cm. The pressures fell immediately to the previous levels. Two other coughs were produced (*b* and *c*), with the same effects. The conditions continued as they were before coughing.

F. Obstruction: Lobular and Simple Inspiratory (Fig. 2, *B*).—Begun at Height of Expiration (Observed Twenty-five Minutes): Figure 16 shows that at first the distal pressure at expiration was 1.2 cm. of water; the proximal pressure, 0.1 cm. (Only these pressures

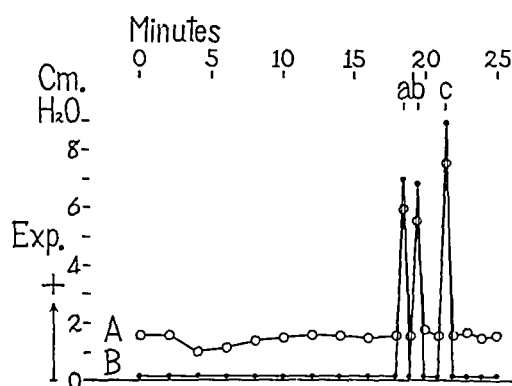


Fig. 15.—Total, lobular obstruction (see plan, fig. 2, *A*). *a*, *b* and *c* indicate single coughs of various intensities. The designations are the same as in figure 13.

are important here.) There was no important change for fifteen minutes. Air bubbled heavily at the valve (leaving the lung) with each expiration throughout. One very forceful cough was produced (*a*). The distal pressure rose sharply to 12 cm. of water; the proximal pressure, to 14 cm. Air bubbled unusually heavily. The pressures fell immediately to the previous levels. One harder cough was produced (*b*). Pressures rose a little higher and a little more bubbling occurred than with the first cough. They returned to the previous levels and remained there.

G. Obstruction: Lobular and Simple Expiratory (Fig. 2, *C*).—Begun at Height of Expiration (Observed Twenty-seven Minutes): Figure 17 shows that at first the distal pressure at expiration was 3 cm. of water; the proximal pressure, 0.3 cm. (Only these pressures are important here.) There was no important change for eighteen minutes. Air bubbled heavily at the valve (entering the lung) with each

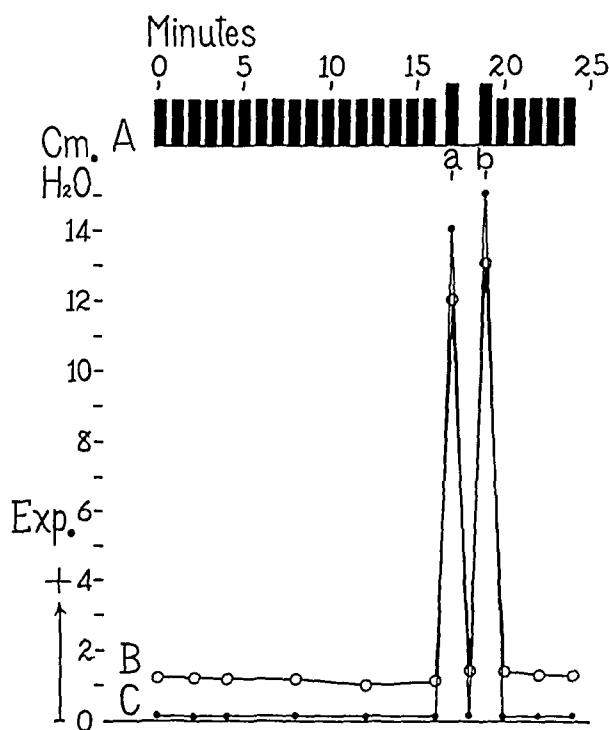


Fig. 16.—Simple inspiratory, lobular obstruction (see plan, fig. 2, *B*). *a* and *b* indicate single coughs, consecutive and very intense. The designations are otherwise the same as in figure 14.

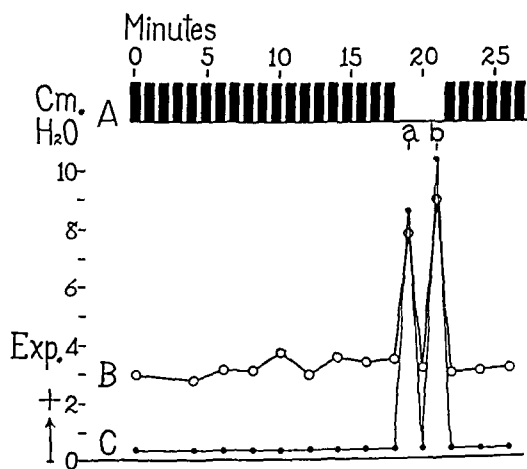


Fig. 17.—Simple expiratory, lobular obstruction (see plan, fig. 2, *C*). Single coughs of different intensities are indicated by *a* and *b*. The designations are the same as in figure 14.

inspiration throughout. One cough was produced (*a*). The distal pressure rose sharply to 8 cm. of water; the proximal pressure to 8.6 cm. There was no bubbling. The pressures fell immediately to the previous levels. One harder cough was produced (*b*). The pressures rose a little higher than with the first cough. They returned to the previous levels and remained there, and bubbling occurred as before coughing.

CONCLUSIONS

FREE BREATHING

In all varieties of bronchial obstruction the intrabronchial pressure distal to the point of obstruction oscillates with respiration about the level of atmospheric pressure, rising above it in expiration and falling below it in inspiration. The intrabronchial pressure proximal to the obstruction oscillates in a similar manner but much less widely. Accordingly, at expiration the distal pressure is higher than the proximal pressure, and at inspiration the relationship is reversed. The deeper the respirations are, the greater are the oscillations of the distal pressure and the greater the differences between the two pressures. The zone of oscillation of the distal pressure shifts up and down on the scale of pressures with increases and decreases in the degree of inflation of the obstructed part of the lung. Thus, if the obstructed part contains tidal air (obstruction begun at height of inspiration), the zone lies high, with the expiratory pressure extending markedly above the atmospheric level and the inspiratory pressure falling only slightly below that level; if tidal air is partly, or entirely, missing (obstruction begun during expiration or at its height), the zone is lower and the expiratory pressure is only slightly above the atmospheric level; and if all of the tidal air and part of the residual air are lacking (absorbed after obstruction), the zone is still lower and lies entirely below atmospheric pressure. The intrapleural pressure oscillates with respiration in the same manner and to about the same extent as the distal intrabronchial pressure but at much lower and subatmospheric pressures. These pressures present, also, certain special forms of behavior which are characteristic of the various types and positions of bronchial obstruction. Different forms of behavior occur because the obstructed and free parts of the lung develop different conditions of inflation. The obstructed part becomes differently inflated in all forms of bronchial obstruction, because air enters or leaves the obstructed part with reduced facility. In those forms of obstruction in which the air tends to be absorbed without being constantly replenished the differences of inflation are particularly great. The special forms of behavior are as follows:

In total, lobar bronchial obstruction the zone of oscillation of the distal intrabronchial pressure changes only as a result of absorption

of the air. If the zone is high to begin with (tidal air included) it starts to fall very soon and within a few minutes it comes to rest at a level with the expiratory pressure slightly above atmospheric pressure (characteristic position when tidal air alone is lacking).¹⁵ This level may be maintained for several hours. If the zone is low to begin with (tidal air excluded), it suffers no change for several hours.¹⁶

In simple inspiratory, lobar obstruction any tidal air that may be included in the obstructed part of the lung to begin with escapes quickly past the valve, and the zone of oscillation of the distal intrabronchial pressure falls in pace with the loss of air. When that air is gone, no more passes the valve and the obstruction becomes total in effect, with the pressure levels stationary, as described in the preceding paragraph. The obstructed part is not collapsed by the action of the valve.

In simple expiratory, lobar obstruction air enters rapidly through the valve, until the obstructed part has reached its capacity for air, and then only a little enters from time to time.¹⁷ The zone of oscillation of the distal intrabronchial pressure rises in pace with the accumulation of air, and when the capacity for air is reached, the zone remains stationary. The expiratory limit of the zone may reach nearly any height, depending on the degree of expiratory effort; and the inspiratory limit may rise above atmospheric pressure. The thoracic parietes expand automatically to accommodate the inflated parenchyma and to maintain the original range of respiratory movement. The intrapleural pressure is thus kept unchanged. As additional evidence of this automatic accommodation is the fact that, if the animal is killed at this time, both the distal intrabronchial and the intrapleural pressures rise markedly. The obstructed part is emphysematous.

In the three types of lobular obstruction collateral respiration saves the obstructed part of the lung from such alterations of inflation as develop in lobar obstruction. Accordingly, if the obstruction is valvular, air enters or leaves by the valve (depending on the type of valve) with every respiration for indefinitely long periods, and escape or supply

15. The fall in pressure is probably due to the absorption of tidal air from the obstructed part of the lung. The stationary condition after that is interpreted as indicating an extremely slow absorption of the residual air, or no absorption at all, for the time being. Other work (Van Allen, Lindskog and Richter [footnote 8, first reference]) has shown that when the residual air is absorbed and atelectasis is produced, the distal intrabronchial pressure falls markedly below atmospheric pressure. The intrapleural pressure falls markedly also (Elkin, D.: *Ann. Surg.* 86:885, 1927, and previous reference).

16. Four hours was the longest period of observation of these pressures.

17. This is apparently only just enough to make up for absorption.

of air by collateral connections proceeds concurrently, so that the pulmonary inflation and pressures stay the same.¹⁸ The obstructed part becomes neither collapsed nor emphysematous.

COUGHING

Cough is accomplished during expiration and has two phases.¹⁹ The first phase begins with the onset of effort to expire. The tracheal passage is blocked completely (by adduction of the vocal cords in natural cough and by artificially applied occlusion of the tracheal outlet in these experiments) and the intrabronchial and intrapleural pressures rise sharply. The second phase begins after a moment with sudden opening of the trachea. The imprisoned air escapes explosively, and the intrabronchial and intrapleural pressures fall. The height to which the pressures rise in the first phase is in proportion to the inflation of the lung as a whole to begin with and to the expiratory effort. In general, the principles that have been described for free breathing apply also to cough, as follows: The object obstructing the bronchus lies between two pressures of air during cough, the relationship between which is determined by the relationship between the inflations of the obstructed and free parts of the lung. These relationships may be changed, even reversed, at any instant in cough. Since the direction in which the intrabronchial impulses tend to displace the obstruction must be that of the action of the greater impulse and the force is the difference between the two impulses, the displacing influence of cough is variable as to both direction and force, even with a constant degree of expiratory effort. In succeeding paragraphs are given the relationships between the inflations of the two parts of the lung and the directions of the displacement that the obstruction may undergo in the two phases of cough, for the varieties of bronchial obstruction.

In total, lobar obstruction the inflation of the obstructed part during the first phase of cough may be the same or less than that of the free part, depending on whether or not tidal air is contained in the obstructed part at the onset of the act. According to this circumstance, then, there is no displacing impulse or there is one directed toward the alveoli. During the second phase, as air is discharged from

18. Other work (Van Allen and Adams [footnote 7]; Van Allen, Lindskog and Richter [footnote 8, first reference]; Van Allen and Lindskog [footnote 8, third reference]; Adams [footnote 10]) has shown that the absorption of air from the obstructed lobules is also compensated for by collateral respiration.

19. It seems more logical to describe cough as confined entirely to expiration, rather than to include the preceding inspiration as the first phase of the act, as is commonly done. Indeed, cough may be accomplished with all its essential effects from a state of respiratory rest and without any additional preliminary inflation of the lung.

the free part and the inflation of that part falls, the relationship between the inflations changes rapidly. Thus, if the obstructed part contains tidal air in any amount at all at the beginning of the cough, its inflation quickly becomes the greater and a displacing impulse develops which is directed toward the trachea. If the obstructed part has no tidal air but has a full amount of residual air at the beginning of the cough, its inflation quickly becomes equal to that of the free part and there is no displacing impulse. If, finally, the tidal, and a part, or all, of the residual air is missing from the obstructed part, its inflation remains the lesser, and there is a displacing impulse directed toward the alveoli.

In simple inspiratory, lobar obstruction the obstructed part rapidly discharges any tidal air that it may contain, and its inflation becomes and remains less than that of the free part (except at the end of the second phase of cough when tidal air is entirely lost also from the free part and the inflations become the same). Throughout the act, then, there is a displacing impulse directed toward the alveoli.

In simple expiratory, lobar obstruction the obstructed part rapidly gathers tidal air, and its inflation becomes and remains the greater. Throughout the cough, then, there is a displacing impulse directed toward the trachea.

In the three types of lobular obstruction the obstructed part receives and gives off air with respiration (either by collateral respiration alone or both by that means and by valve), but less freely than does the free part. During the first phase of cough the inflation of the obstructed part is slightly the lesser and there is a displacing impulse directed toward the alveoli. In the second phase the inflation of the obstructed part quickly becomes the greater, and there is a displacing impulse directed toward the trachea.

COMMENT

A type of bronchial obstruction which is not referred to is one in which the bronchial lumen is incompletely occluded during both periods of respiration. It occurs spontaneously in clinical patients from the presence of a small mass of viscid mucus or inspissated pus on the wall of a bronchus, from a neoplasm partially filling or compressing a bronchus, or from an inflammatory swelling of the bronchial wall.⁶ The aerodynamics of this type of obstruction was investigated, but description of the experiments and the results are not given, because the subject was found to be so simple as not to warrant separate detailed presentation. The method was the same in principle as that used for the other work, except that the dilatable cannula was replaced by one that only partially filled the bronchus. The aerodynamics of partial bronchial obstruction was found not to be influenced by the factors—

position of obstruction, absorption of air and collateral respiration—that may affect total and valvular forms of obstruction. Air passed the obstruction at each period of respiration but with somewhat less facility than through the normal bronchial passage. Accordingly, the intra-bronchial pressure distal to the obstruction in expiration was greater than that proximal to it, and in inspiration it was less. The differences in the two pressures were in proportion to the extent of the obstruction, and to the depth of breathing, but they were not so great as in total obstruction. Cough invariably produced an impulse with a tendency to drive the obstruction toward the trachea, and this occurred during the second phase of the act.

In many essential respects the aerodynamics of bronchial obstruction depends on the simple anatomic fact that the passages on both sides of the obstruction communicate directly with, and receive air from, parts of the lung, and on the principle arising from this fact, that the pressures in the passages proximal and distal to the obstruction have the same relationship to each other as the inflations of the parts of the lung proximal and distal to the obstruction. The period and the force of respiration do not primarily determine these pressure relationships. Bronchial obstruction is thus differentiated from tracheal, laryngeal and upper respiratory obstruction, for in the latter the lung lies entirely on one (the distal) side and the pressure on that side alone may be expected to change with respiration. There, the distal pressure is necessarily the greater at expiration and the proximal pressure (atmospheric pressure) is the greater at inspiration. It is to be noted that the conditions of bronchial obstruction in the experiments held to the anatomic circumstance mentioned, for the passage on one side of the obstruction led to the occluded part of the lung and that on the other side to the free part.

The problem referred to at the beginning of the paper, namely, the inconstancy of the effects of cough on substances contained in the bronchi, can now be better understood. The experiments show that alterations of the direction of the cough impulse may take place at nearly any instant during cough and from cough to cough. The influences that determine the direction of the impulse are not such as to be disclosed at ordinary bedside or fluoroscopic examination of the chest, and to the clinical observer the effects may well appear to be inconsistent. A point to be kept in mind concerning the action of cough is that it depends for aerodynamic eliminative effect on the presence of tidal air in some quantity in the lung distal to the obstruction. Just as the cough produces no external explosion when the lung as a whole contains no tidal air, so also cough obtains no explosion from a single bronchus unless the part of the lung supplied by that bronchus contains tidal air.

The results of the experiments furnish an answer as well to the other problem, as to whether an object obstructing a bronchus may produce atelectasis by acting as a valve and discharging the imprisoned air. Atelectasis cannot be produced in this way, under the natural conditions of bronchial obstruction. The object may, indeed, act as a valve, but it discharges air only as long as tidal air remains in the obstructed part of the lung, which is for a period of a breath or so at the most in lobar obstruction and for an indefinitely long period (while collateral respiration continues to supply the part with tidal air) in lobular obstruction. The development of atelectasis is hastened to the extent that the tidal air is eliminated, but it must await removal of the residual air by the slower process of absorption. Those who favor the theory of exhaustion of air by valvular action suggest that the residual air is "milked" past the valve. They point out that the obstructed segment of lung must be pressed on from the sides by the free and fully inflated portions when the individual makes effort to expire. The present experiments showed, to be sure, that the obstructed part is so pressed on and that the pressure in the passages distal to the obstruction is raised thereby, but they showed, too, that this cannot expel the residual air through the valve, because pressure is being exerted at the same time on the proximal side of the valve. The fact is that the pressure obtained on the proximal side of the valve is greater than that on the distal side. This is so regardless of how great the effort to expire may be (tidal air being absent from the obstructed part of the lung). Only when the natural anatomic relationships of the bronchi, just referred to, have been altered, may the residual air be "milked" past the valve. This occurred in the original experiment of Van Allen and Adams with a water valve, for the proximal side of the valve was given no connection with the free part of the bronchial tree. When the animal strained to expire with each breath, the pressure on the proximal side (atmospheric pressure) remained constant, the pressure on the distal side was raised, and the residual air was expelled. An artificiality with the same effect was probably present, also, during the bronchoscopic observations of Jackson referred to. The bronchoscope acted as a cannula. It reached into the obstructed bronchus, separating it to some extent from the other bronchi and connecting the outer face of the valvular obstruction directly with the outside. Its presence in the larynx and trachea probably interfered somewhat with the respiration of the free parts of the lung. Accordingly, when the individual strained to expire, the pressure on the distal side of the valve at expiration may well have been higher than that (atmospheric pressure) on the proximal side, the result of which would be to expel some of the residual air through the valve with every breath. One infers from Jackson's descriptions of the valves that

some of them at least were situated in large lobular bronchi; and in these cases another explanation suffices. In lobular obstruction under any of the circumstances valvular action may continue indefinitely; however, without producing atelectasis.

The condition that Jackson and Lee²⁰ described clinically and termed obstructive emphysema was reproduced experimentally in this work for the first time. As was noted in their patients, so also in these animals, the condition depended on the presence of a valvular type of obstruction in a bronchus, with the effect of allowing the obstructed part to inspire only. Air accumulated faster than it could be absorbed, and the parenchyma became overdistended. One contribution to the subject was made here, for it was found that obstructive emphysema occurred only in lobar obstruction. When the bronchus of a group of lobules alone within a lobe was obstructed with a valve of this type, collateral respiration removed the air as fast as it entered through the valve and prevented overinflation of the parenchyma.²¹

Lobular obstruction undoubtedly occurs much more frequently than lobar obstruction. A drop of moisture in a capillary respiratory duct must fill the lumen over a considerable length and prevent the passage of air, so that obstruction of this magnitude, at least, probably occurs in most cases of bronchial catarrh. When cough or other expiratory effort takes place right away, the tidal air originally imprisoned must still be present to serve for elimination of the obstruction; but when the subject sleeps or for other reasons remains quiet for a period, absorption proceeds and collateral respiration may compensate for it and maintain a supply of tidal air for the eliminative action of cough when rest ceases. It is, therefore, likely that collateral respiration is important in pulmonary economy. A bronchial tree without provision for collateral respiration would be as inefficient as a blood-vascular system without collateral circulation, perhaps more so since bronchial obstruction is probably more common than arterial obstruction.

It should be remembered that cough appears to have other means of effecting or promoting broncho-elimination than the action of the intrapulmonary currents of air, at least as far as the larger bronchi are concerned. The walls of the larger bronchi contract with expiration and dilate with inspiration. The movements become very marked with vigorous breathing. We have seen in dogs by bronchoscopy that the lumina of tertiary bronchi become totally obliterated when the animals strain to expire, and the same effect has been observed in man.²² It seems probable that these movements aid broncho-elimina-

20. Jackson, C., and Lee, W.: *Tr. Am. S. A.* **43**:723, 1925.

21. It is conceivable that obstructive emphysema might occur in a lobule alone, but this would have to be under conditions with interference to collateral respiration.

22. Weingaertner, M.: *Arch. f. Laryng. u. Rhin.* **32**:1, 1920.

tion, the contraction first serving to mold any soft plastic mass that lies in the bronchus and to squeeze it along the passage, and the dilation then permitting air to be inspired past the mass. Tidal air would thus be provided to the obstructed part of the lung, and subsequent coughing would be rendered more productive. The deep breathing that is advocated clinically for relief from bronchial obstruction obtains the result only in this manner, it would seem, when a lobar bronchus is obstructed; but when a lobular bronchus is affected, both this mechanism and that of collateral respiration may be called into operation to bring air to the affected part. Indeed, as regards the action of collateral respiration, experiments²³ have shown that deep breathing markedly increases the rate of transmission of air to and from obstructed lobules. The transmission has been found to cease altogether in very shallow breathing.

SUMMARY

The principles of behavior of the intrapulmonary pressures and currents of air in bronchial obstruction were investigated in a series of experiments. The various types and positions of obstruction that have been described in man and the forms of breathing that accompany them were reproduced in dogs, and the air pressures and currents were measured and observed directly. The behavior was found to be consistent and to follow certain rules, so that principles of aerodynamics of bronchial obstruction were formulated. Of particular interest was the difference that was found between the aerodynamics of lobar and lobular obstructions. Collateral respiration was found to be responsible for this difference. The results of the study also afforded clarification for certain obscure clinical phenomena of bronchial obstruction, particularly for the inconstant effects of cough on materials occluding the bronchi and for the relationship between valvular bronchial obstruction and atelectasis. The clinical condition of obstructive emphysema was reproduced experimentally, and knowledge of its nature was advanced.

23. Van Allen, Lindskog and Richter (footnote 8, fourth reference).

SO-CALLED FIBROSARCOMA OF BONE

BONE INVOLVEMENT BY SARCOMA OF THE NEIGHBORING SOFT PARTS *

CHARLES F. GESCHICKTER, M.D.

BALTIMORE

The osteogenic portions of the bone do not give rise to sarcoma of the true fibrospindle cell type, the connective tissue tumors arising in this structure being either fibroblasts of the fibro-osseous series with a tendency to true bone formation (fig. 1) or precartilaginous connective tissue destined to form bone via the intracartilaginous route (fig. 2) (Geschickter¹). Fibrospindle cell sarcoma arising in either the outer layers of the periosteum or in the adjacent soft parts may, however, invade the osseous substance and give rise to a tumor in which the predominant manifestations on physical or roentgenologic examination are related to the bone. Such bone involvement, by direct extension from the soft parts, is clinically very confusing, particularly when the bone changes are extensive, and even at operation or after pathologic examination of the tissue, is usually misinterpreted as a primarily osseous lesion.

While from a pathologic standpoint this group of tumors usually has a structure indicating a connective tissue origin, the current conception that these fibrosarcomas that invade the bone are all products of the nonosteogenic layers of the periosteum is erroneous. These tumors, on the contrary, are far more variable in origin and may arise either from this investing portion of the periosteum or from a similar connective tissue or fascia, investing muscles, vessels or nerve trunks in the overlying soft parts. In fact, in the present series of fifty cases clinically grouped under the heading of fibrosarcoma of the bones, new growths with an origin in these various structures are all represented. The largest group of these neoplasms (thirty-one) show a histologic composition of fibroblasts, spindle cells or small oat-shaped cells, relating them to a single cycle of development in connective tissue concerned with the fibrous portions of the outer periosteum, the fascia or the fibrous portion of nerve trunks or vessels. This group, which may be

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* From the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University.

1. Geschickter, C. F.: Fibrocartilaginous Tumors of Bone, Arch. Surg., to be published.

termed the fibrospindle cell series, is a true pathologic entity and may be graded in its malignancy according to the degree of differentiation shown by the predominating cells. A more varied and smaller group of these neoplasms must be differentiated from this larger fibrospindle cell series. In this small group, a careful analysis of the histologic structure shows the tumor to be arising from neurogenic elements



Fig. 1 (path. no. 36784).—Fibroblastic tissue in bone laying down osteoid spicules in response to a low grade infection. The fibroblasts are transforming into osteoblasts which are applied to the surface of bone newly formed from fibrous tissue.

(neurogenic sarcoma) or from the muscle (rhabdomyosarcoma) or probably from vessels (angioma), and hence the type of treatment and prognosis must be correspondingly different. This small and miscellaneous group of tumors, despite a varied source of origin, may secondarily implicate the bone because of a proximity to this structure.

The present study, therefore, is to show that the histologic composition in the new growth is a more reliable index to its clinical and pathologic behavior than is the anatomic location or apparent relationship to bone. Assumptions regarding prognosis or treatment based on proximity to bone disclosed by the x-rays or at exploration, or based on the gross resemblance of the neoplasm to a fibroid substance are

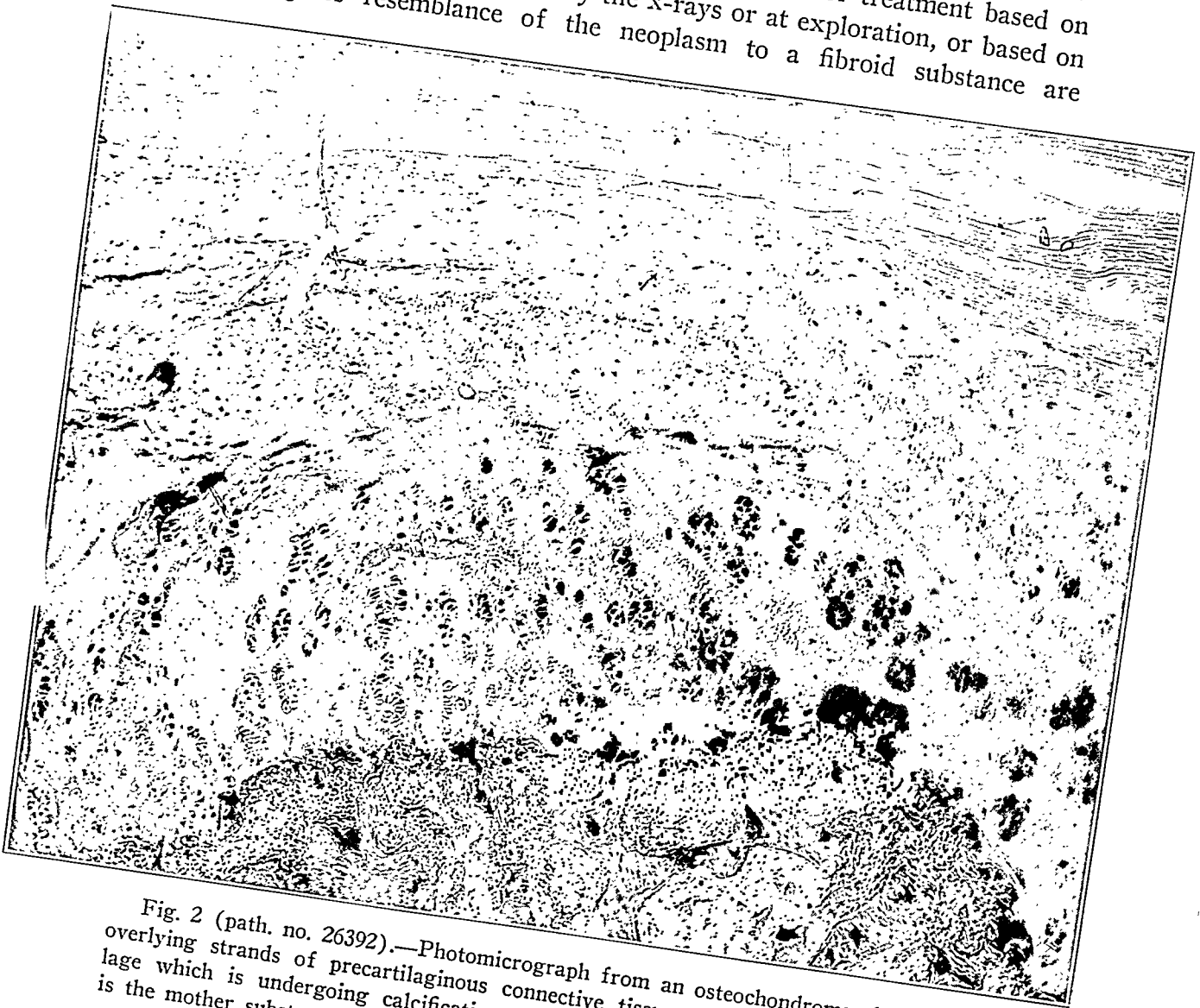


Fig. 2 (path. no. 26392).—Photomicrograph from an osteochondroma showing overlying strands of precartilaginous connective tissue transforming into cartilage which is undergoing calcification. This precartilaginous connective tissue is the mother substance responsible for the resulting osteochondroma.

untrustworthy in this group of neoplasms. But conclusions can be drawn with a fair degree of accuracy after microscopic examinations which permit the lesion to be classified in either the fibrospindle cell group, the neurogenic group or among tumors derived from other soft part structures, and which also allow of a definite grading according to the degree of cellular differentiation.

TUMORS OF THE FIBROSPINDLE CELL GROUP

Invasion of the bone from without, through direct extension by a tumor of nonosseous origin usually indicates the presence of a sarcoma of the fibrospindle cell group. Such bone involvement is of relatively infrequent occurrence and is recorded in this laboratory in only about 1.5 per cent of the cases among seventeen hundred neoplasms involving bone. The majority of the sarcomas in this group are not of a high degree of malignancy, and the life of the patient can usually be safeguarded if the proper diagnostic and therapeutic measures are carried out in time.

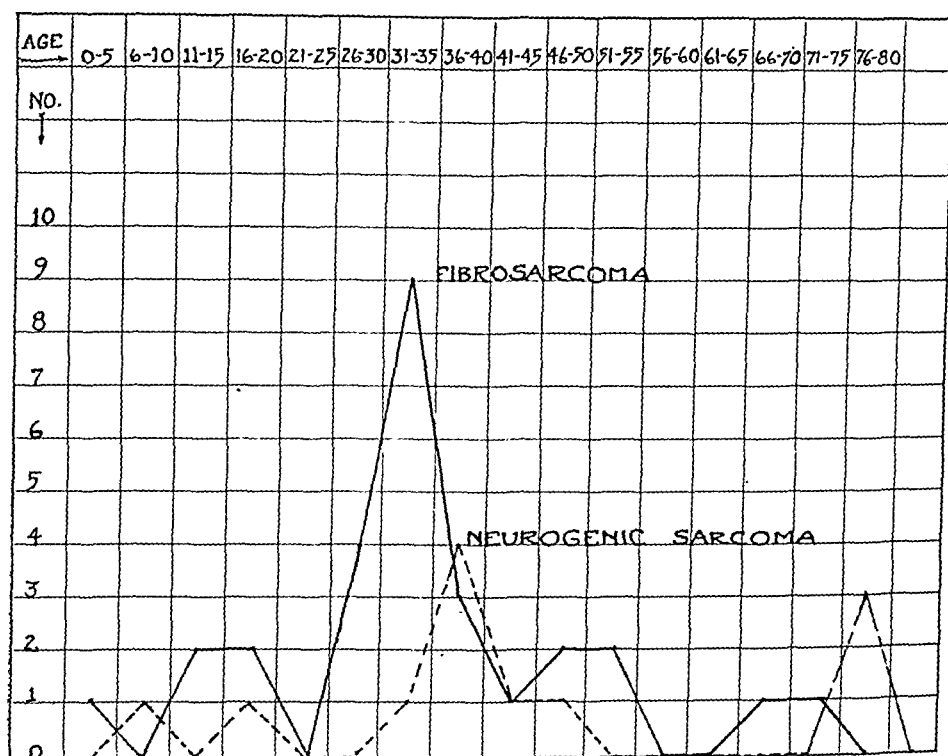


Fig. 3.—Chart showing the age incidence in thirty-eight cases of so-called fibrosarcoma of the bone. The solid line indicates the tumors of the fibrospindle cell series; the broken line, tumors of the neurogenic series.

Clinical Features.—Fibrospindle cell sarcoma is a disease of adult life, occurring most frequently beyond the age of 30. The age incidence is remarkable for a sarcomatous tumor and parallels more closely the distribution of carcinomas among adults. The lower extremity is usually the site of predilection, the region of the femur being most often involved. More rarely the upper extremity may be implicated, and in exceptional instances the new growth may overlie the skull or ribs or be found within the pelvis (figs. 3 and 4, tables 1 and 2). The patients thus affected give a history of a condition of about one year's duration beginning with pain of increasing severity and followed by the

appearance of swelling and then by dysfunction of the limb. In several instances a pathologic fracture occurred.

The swelling is smooth in contour and differs from the ordinary type of soft part sarcoma in the depth of its location and in its firm attachment to the underlying bone. Interference with function is also more rapid in the affected limb because of this proximity to bone. The tumor growth is fairly rapid and steadily progressive, producing a

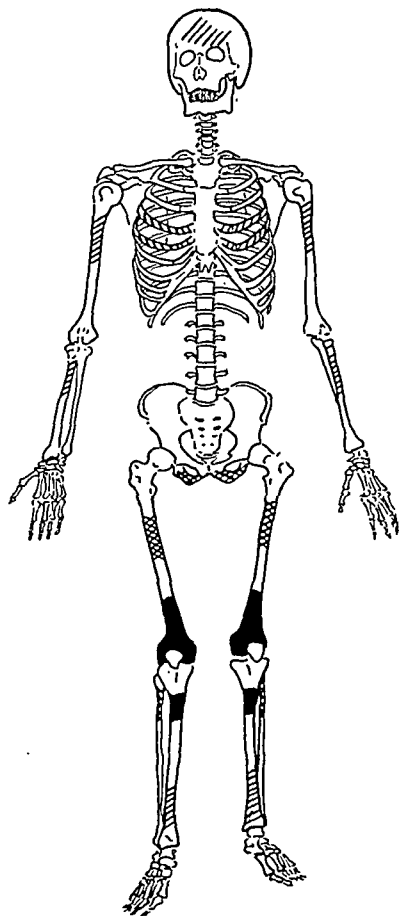


Fig. 4.—Chart showing skeletal distribution in thirty-eight cases of fibrosarcoma and neurogenic sarcoma of the bone. The black areas indicate the most frequent sites; the checked areas, the common sites and the diagonal lines, the rare or occasional sites.

mass of firm or rubbery consistency. When the swelling is situated near the end of a bone, the growth may extend across the joint and ultimately involve a neighboring bone, a type of invasion that is exceedingly rare in truly osteogenic tumors. Although the regional lymph nodes may be enlarged, metastases to the lymph glands has not been microscopically proved in these cases and probably does not occur.

TABLE 1.—Differentiated Forms of Fibrospindle Cell Sarcoma

Path. No.	Race	Sex*	Age	Location	Duration, Mo.	Symptoms	Röntgenologic Picture	Treatment	Microscopic Picture	Result
38182	W	♀	46	Femur	Soft part shadow, some bone destruction	Amputation, July 14, 1926	Spindle cell	Well 9 mo.
37113	O	♀	20	Femur, upper tibia,	..	Pain, tumor	Soft part shadow, some secondary bone destruction	Excision, April 6, 1925; radium	Fibrospindle cell	Well over 2 yr.
35750	W	♂	43	Femur, upper	17	Pain	Slight bone involvement	Curettement, Aug. 9, 1924; radium in wound	Fibrospindle cell	Dead 8 mo. following operation
35023	W	♀	30	Femur, lower	3	Tumor	Secondary bone destruction	Excisions, 1914 and 1918; amputation, 1928	Spindle cell	Dead 10 yrs. following first excision
32906	33	Femur	12	Pain, swelling; 6 mo.	Exploration, Jan. 25, 1919; x-ray, radium, March 13, 1919	Fibrosarcoma	Well 11 yrs. following exploration
32997	O	♀	55	Humerus, upper	36	Pain, trauma, tumor	Exploration, May 3, 1923	Fibrosarcoma
31267	W	♀	34	Skull	2½	Slight pain, tumor	Secondary bone destruction	Exploration, Oct. 14, 1922	Spindle cell	Dead 5 yr. later
29401	W	♀	..	Leg (knee)	36	Trauma, tumor	Large soft part shadow	Amputation, Nov. 19, 1921; amputation following 2 excisions; x-ray and radium	Fibrospindle cell	Well 8 yr., 5 mo. later
29259	...	M	..	Ankle region	..	Tumor	Soft part shadow, secondary bone destruction	Exploration, April, 1920; partial excision, April, 1920; x-ray	Spindle cell	Well 13 yr. following first operation
29240	W	♂	40	Scapula	..	Tumor	Soft part shadow	Excision, September 1920, excision of recurrence May 23, 1921; x-ray, radium	Fibrospindle cell	D'sense progressing (11 yr.)
28189	W	♀	33	Scapula	1	Tumor	Excision, excision of recurrence, November, 1911; x-ray	Fibrospindle cell	Well 3 yr. following second operation
27884	W	♀	33	Ribs, 5th and 6th	..	Tumor	Exploration, Feb. 1, 1921; resection, Feb. 4, 1921	Fibrosarcoma	Well nearly 10 yr. following second operation
27752	W	♀	34	Femur, lower	24	Tumor, pain limp, 1 yr.	Periosteal shadow with bone destruction	Amputation, Sept. 24, 1920	Fibrospindle cell	Dead 9 yr. following resection
27555	W	♂	49	Radius, lower	12	Tumor following 4 fractures	Extensive bone destruction	Radium, October, 1920; curettement; amputation for recurrence, Feb. 12, 1921	Fibrospindle cell	Well over 9 yr. later
27347	W	♂	..	Femur, lower	12	Tumor	Soft part shadow, some secondary bone destruction	Amputation advised	Fibrosarcoma	Dead 14 mo. following onset; (tuberculous pneumonia)
26884	W	♂	29	Fibula, shaft	48	Trauma, pain, tumor	Periosteal shadow, some bone destruction	Exploration, January, 1917 (5 mo. following onset); gold therapy January, 1919; exploration, August, 1920; amputation, Nov. 22, 1920	Fibrospindle cell	Well almost 9 yr. following amputation
26877	W	♂	30	Tibia, upper	..	Intermittent pain	Amputation, Feb. 14, 1920	Fibrospindle cell	Well 6 yr. later
25453	W	♂	53	Femur, lower	14	Pain, tumor	Lungs, normal; periosteal tumor mass; small amount bone destruction and bone formation	Amputation, May 20, 1919	Spindle cell	Well over 8 yr.
24536	W	♂	58	Femur, upper	17	Weakness, tumor	Soft part shadow, extension secondary bone destruction	Amputation, July 5, 1918	Fibrosarcoma	Well almost 12 yr. later
23407	W	♀	29	Femur, lower	10	Trauma, tumor, dysfunction of knee	Soft part shadow, much destruction secondary bone destruction	Exploration, April 22, 1922; amputation, April 27, 1922	Spindle cell	Lost
15722	W	♂	12	Tibia, upper	3	Pain, swelling, tenderness	Exploration, Sept. 2, 1908; subsequent resection	Spindle cell	Dead 11 yrs. later
Surg. No. 9203 (4666)	O	♂	19	Femur, lower	30	Trauma, joint of fusion; 2d trauma, pain; swelling	Soft part shadow, extensive bone destruction

Roentgenologic Features.—Fibrosarcoma affecting bone resembles other forms of sarcoma of the bone in its tendency to occur as a single lesion and to involve the regions of the lower end of the femur or upper end of the tibia. It differs from other malignant periosteal tumors in the size and character of its soft part shadow and in its tendency to destroy the bone from without, inwardly. The one constant feature in the roentgenogram is this extra-osseous soft part shadow which is

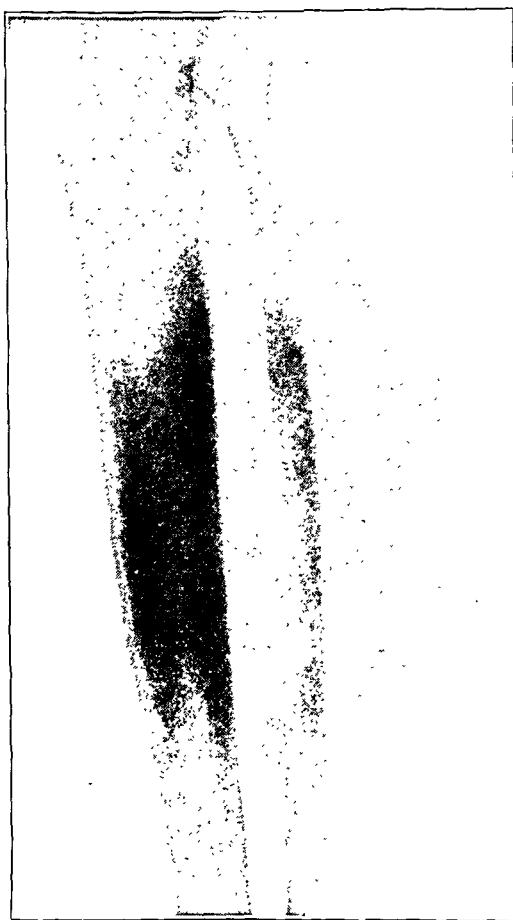


Fig 5 (path. no. 26884).—Roentgenogram of a typical case of fibrosarcoma involving the shaft of the fibula. There is a large soft part shadow, producing a faint periosteal reaction and splitting of the cortical layers of the bone. The patient was a white man, aged 29, giving a history of trauma, pain and tumor formation of twelve months' duration. Amputation was advised in this case. The patient died of a tuberculous pneumonia fourteen months after examination.

more opaque than the cartilaginous masses seen in periosteal chondrosarcoma and less dense than the true bone formation seen in osteogenic sarcomas.

The reaction of the underlying bone to the presence of the tumor is more variable. In the most easily recognized cases the bone is melted

away from without, inwardly with little or no periosteal reaction (figs. 5 and 6). In less typical cases strands of the periosteum which are split and raised may show varying degrees of ossification, but these are never dense or conspicuous (fig. 7). Calcification in the tumor substance is not the rule and is more typical of an aneurysm, an old abscess of the soft parts or of a rare chondroma associated with some bursa in the region of the joints. Occasionally, however, when the fibrous



Fig. 6 (path. no. 23407).—Anteroposterior and lateral views of a low grade of fibrosarcoma involving the lower end of the femur of a white woman, aged 29, who gave a history of trauma, tumor and dysfunction of ten months' duration. The patient is alive twelve years following a primary amputation. Note the large soft part shadow and the bone destruction resulting from invasion of the osseous substance from without. The microscopic structure of this tumor is shown in figure 22.

growth has become large and is not extremely rapid or after a course in deep roentgen therapy, a slight degree of calcareous stippling will be observed.

The size of the soft part tumor which exceeds the area of bone destruction is a helpful diagnostic point. Usually the extra-osseous shadow is large before much evidence of bone destruction is found. Occasionally, however, rarefaction and invasion of the marrow cavity is also pronounced so that there is a resemblance to metastatic carcinoma or osteolytic sarcoma of the osteogenic type (fig. 6). In such instances, however, the size of the soft part shadow, the disappearance of the cortex and the asymmetrical erosion of the marrow cavity gives evidence



Fig. 7 (path. no. 25453).—Anteroposterior and lateral views of a fibrospindle cell sarcoma which is invading the bone. The soft part shadow has an unusual amount of calcified and osseous markings, most of which are due to the splitting and raising of the periosteum. The patient was a white man, aged 53, who had suffered with pain and tumor in the lower end of the femur for fourteen months. He has remained well over six years following the primary amputation.

that the bone is being destroyed from an external rather than an internal cause, as in the truly central lesions produced by metastatic carcinoma or the osteolytic variety of osteogenic sarcoma (figs. 8 and 9). Benign giant cell tumor and benign bone cyst should not be a source of confusion since these benign growths give evidence of their central origin by

expanding the shell of cortical bone from within and rarely produce a soft part tumor of any significant size.

Gross Specimens.—At operation, the tumor is generally found to be definitely encapsulated, although occasionally the fibrous tissue is found infiltrating muscle in the same manner in which it erodes and invades the bone. The tumor mass is firm and fibrous in consistency and often has the definite peculiarity of being arranged in whorls and strands



Fig. 8 (path. no. 37088).—A metastatic hypernephroma involving the shaft of the humerus. The area of bone destruction is central in origin and expands the cortex, which is undergoing destruction, symmetrically. There is little or no soft part shadow.

which run in a number of divergent directions. Occasionally the striation of the tumor is more regular (figs. 10 and 11), and in the more rapidly growing neoplasms the mass may be fleshy or colored with hemorrhagic material (figs. 12 and 13).

The kind and degree of bone involvement varies. In some instances the tumor mass may be shelled away from the bone, and the remaining

osseous surface may be cleaned readily with the knife. In other instances the cortex has disappeared, the cancellous substance is invaded and broken and the central portion of the bone involvement discolored by hemorrhage. In rare instances, when the tumor is relatively benign and slow in growth, the entire cortex is melted away, the marrow cavity invaded, but the neoplastic tissue is sharply demarcated from the firm reactive portions of the remaining bone (fig. 14).

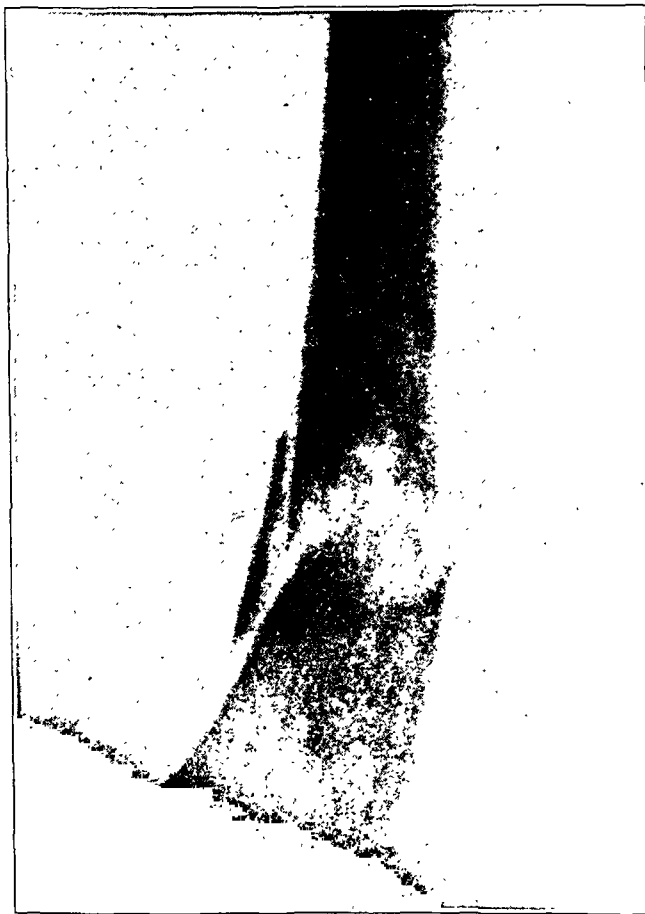


Fig. 9 (path. no. 37614).—An osteolytic sarcoma in the lower half of the femur producing a central area of bone destruction followed by pathologic fracture and escape of the tumor into the soft parts. The extent of the soft part shadow is less than the area of bone destruction.

Dissection of the mass at operation, particularly when the tumor is large, does not often disclose the source of origin. In some instances it is clear that the relationship to the bone is secondary, the tumor shelling out easily and leaving a bare, denuded cortex with little or no evidence of osseous erosion. In other cases the association with the bone is more intimate. The tumor may be definitely attached to the periosteum and invade the cortex, gaining entrance to the marrow

cavity. On entering the marrow cavity it may penetrate up and down the long axis, splitting the bone and causing pathologic fracture. In such cases, the only evidence against a primary osseous origin is the extent to which the soft parts are involved in the region, the degree of extra-osseous involvement indicating that the tumor has had a beginning just without the bone and extended equally in both directions.

In some of the tumors involvement of the joint cavity, extension into adjoining bursae and into the neighboring muscles with involve-



Fig. 10 (path. no. 38182).—Gross specimen of a fibrosarcoma overlying and destroying the lower end of the femur in a white woman, aged 46, which was successfully amputated. The cut surface of the specimen shows clearly the interlacing fibrous bundles, characteristic of this type of fibrospindle cell sarcoma. The microscopic structure is shown in figure 21.

ment of the main nerve trunk or blood vessels suggests that the tumor is primarily of soft part origin.

Microscopic.—Since fibrous tissue derived from an earlier form of connective tissue is common to nearly all organs of the body, the type of fibrospindle cell sarcoma invading bone that has such origin does not

differ histologically from similar tumors in many other locations. Fibrospindle cell sarcoma involving the joint capsule or ligaments, fibrous tumors arising from the outer vessel wall, and fibrosarcoma arising from the fascial planes in and about the muscles are a homogeneous group and differ in their fundamental pathologic process in no essential way from



Fig. 11 (path. no. 25453).—Specimen from the amputated leg in the case shown by roentgenogram in figure 7. The cut surface of the tumor shows clearly the definite fibrous capsule and the relationship to the underlying bone. The cortex is gradually being resorbed, and the tumor has found its way into the marrow cavity. Note the definite striations on the sectioned surface of the new growth, indicating a fibrous structure.

the fibrous new growths arising from the connective tissue framework of many of the internal organs.

It is possible, therefore, to treat these sarcomas of the fibrospindle cell group that secondarily involve the bone along with those arising

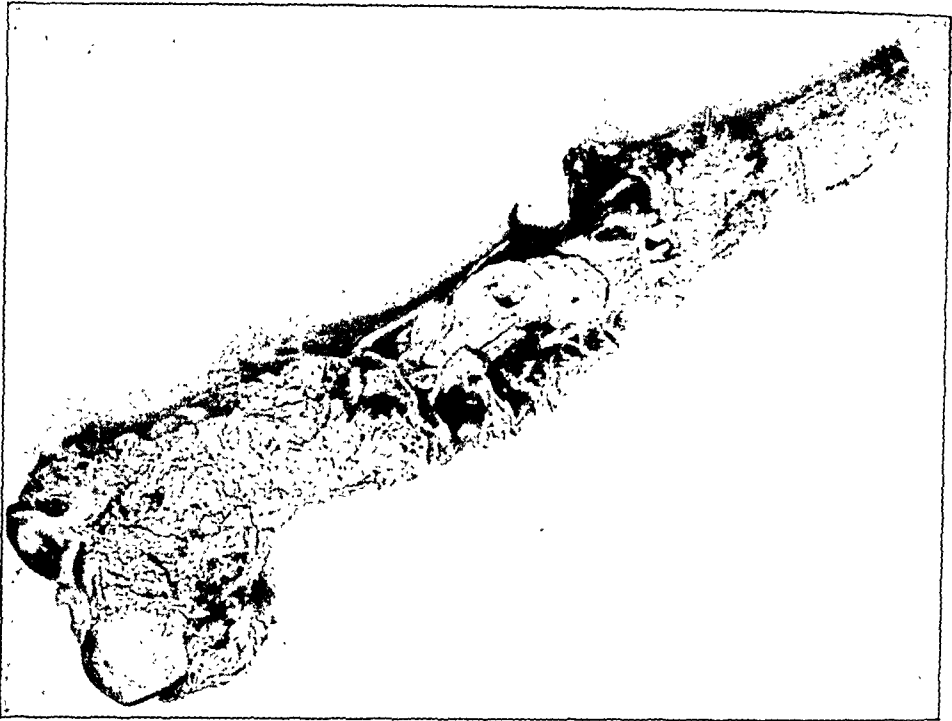


Fig. 12 (path. no. 24536).—Gross specimen of a small spindle cell tumor overlying the femur and invading the shaft of the bone in a white woman, aged 58. The patient has remained well over eight years following an amputation. The fleshy tumor is shown adherent to the periosteum of the shaft of the femur.



Fig. 13 (path. no. 24536).—The tumor mass is shown shelled away from the bone. The glistening fleshy surface indicates the cellular nature of the tumor which is corroborated by sections showing a tightly packed small spindle cell structure.

from the outer layers of the periosteum itself as a single pathologic entity, regardless of the fact that their source of origin in the vicinity of the bone may vary widely.

The microscopic structure of these neoplasms shows a definite cycle of histologic changes. The tumor springs from a small spindle or oat-shaped cell which transforms into a more elongated spindle shape and thence transforms into a prolonged fibroblast with an ever increasing amount of intercellular material of the eosin-staining collagenous



Fig. 14 (path. no. 23407).—Gross specimen from the case shown by roentgenogram in figure 6. The fibroid tumor which is definitely encapsulated is shown invading the bone by pressure necrosis and is clearly demarcated from the neighboring osseous substance. The microscopic structure which resembled a benign fibroma is shown in figure 22.

type. In the more rapidly growing and malignant tumors, the microscopic picture is predominantly of the small plump spindle cell type commonly known as the oat cell. The chief characteristics of this cell are the scantiness of its cytoplasm, the tightness with which it is packed and the tendency for the nucleus to assume a rounded form and to

undergo mitosis so that under high power magnification the cell has a great resemblance to a small round cell sarcoma (figs. 15, 16, 17 and 18).

Oat-shaped cells are sparse among the less malignant tumors which are composed of more truly spindle cells and fibroblasts. When these spindle cells are tightly packed but fairly elongated and arranged in bundles or fasciculae, the type of the tumor may be referred to as a spindle

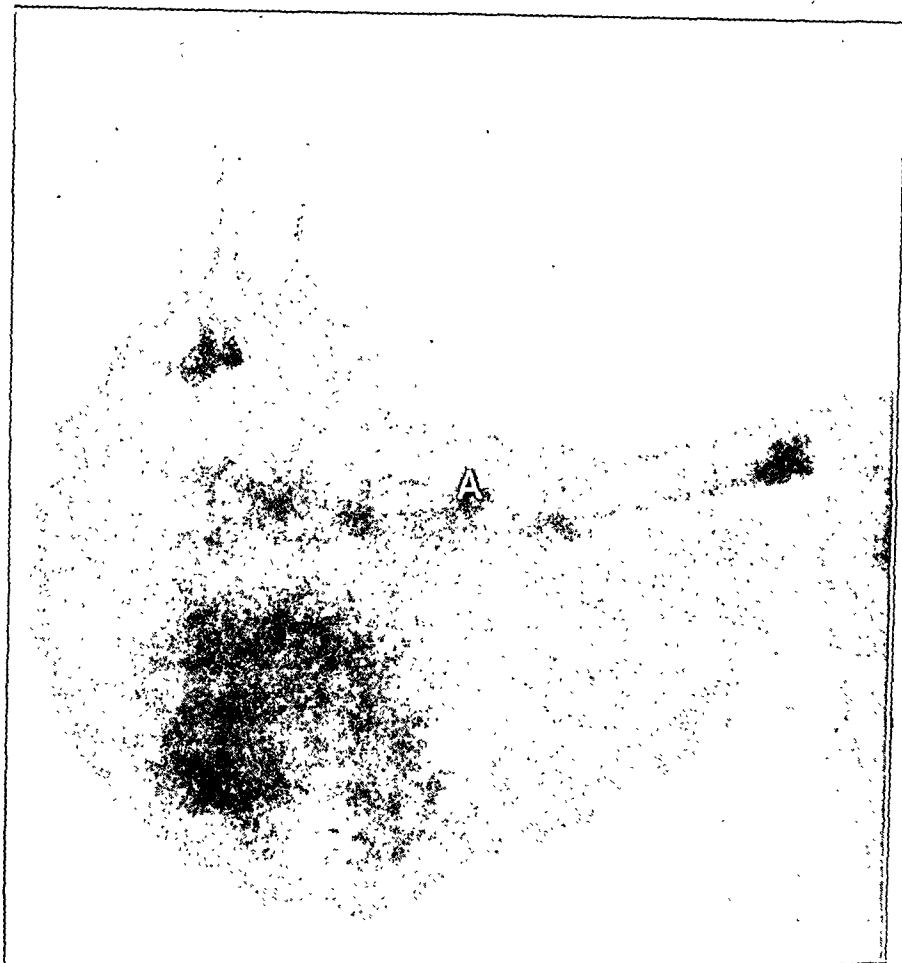


Fig. 15 (path. no. 28276).—A congenital oat cell sarcoma in the lower end of the humerus in an infant 16 days old, who was treated by amputation following an exploratory excision. The patient has remained well over nine years. The roentgenogram shows the large soft part shadow and secondary erosion of the bone resulting in a pathologic fracture.

cell sarcoma (fig. 19). When the spindle cell is replaced in many instances by the fibroblast and there is an increasing amount of intercellular substance, the tumor may be called a fibrospindle cell type (figs. 20 and 21); when the fibroblast predominates and is scattered among a large amount of intercellular collagenous material, the tumor verges on a benign fibroma and may be termed a fibrosarcoma (fig. 22).

This gradual transition from oat cells to spindle cells to fibrospindle cells and to adult fibroblasts permits a definite grading on which a prognosis and the type of treatment may be based, for this transition of cell forms represents the true histogenetic cycle of the tumor. This is evidenced by embryologic studies of the primitive connective tissue surrounding the region of the bone (fig. 23). In this primitive connective tissue the cellular elements are of the oat and spindle cell types



Fig. 16 (path. no. 28276).—The amputated specimen indicating the cellular and hemorrhagic character of the new growth.

with a scanty amount of intercellular substance resembling markedly the less differentiated oat and spindle cell sarcomas.

When the tumors are of the oat cell type with little or no intercellular substance, the neoplasm is exceedingly malignant and warrants the most radical treatment. These oat cell tumors can be readily distinguished from the fibrospindle cell and fibrosarcomas in which there is a greater tendency for whorl formation and a definite amount of collagenous intercellular substance, and the patho-

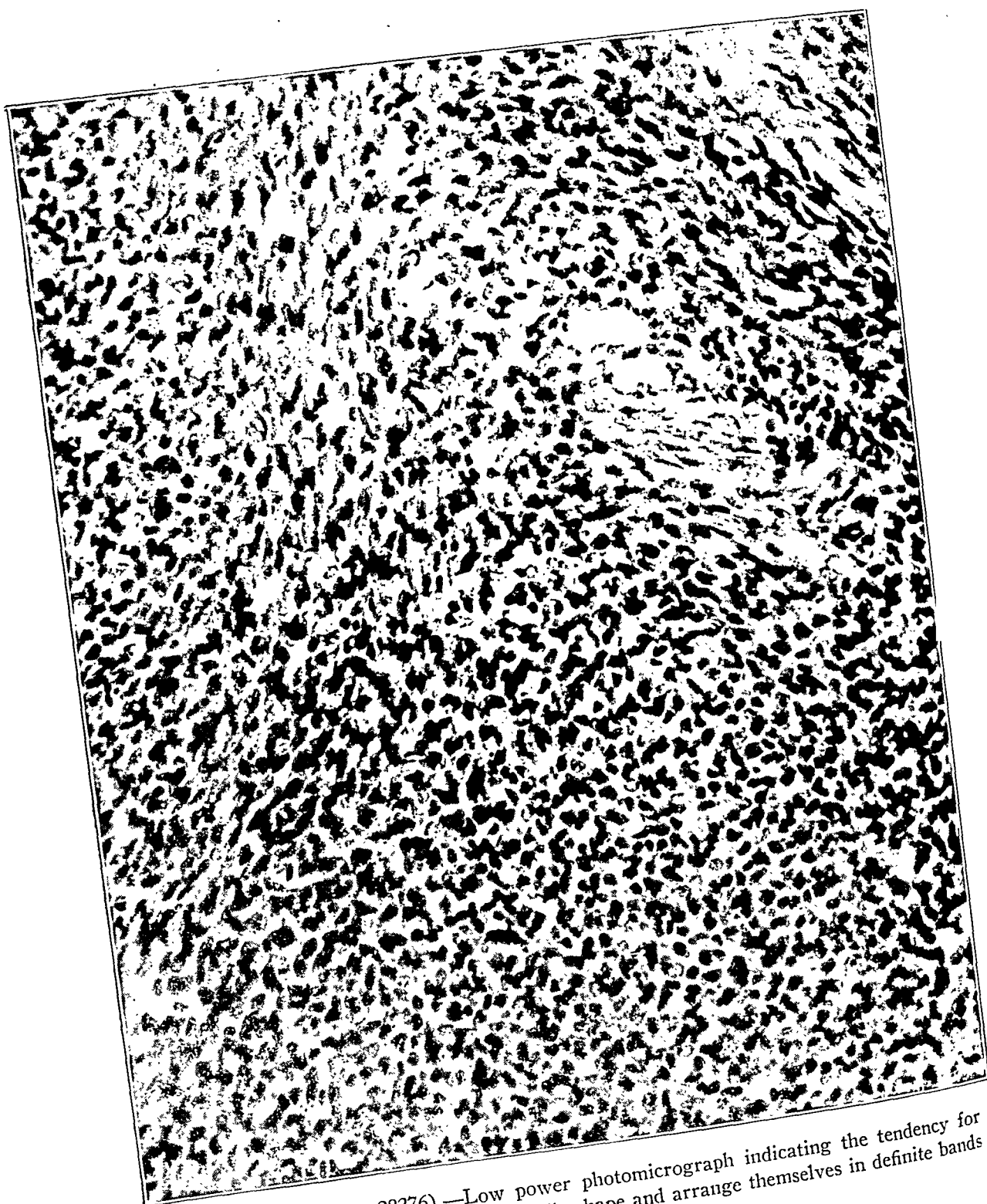


Fig. 17 (path. no. 28276).—Low power photomicrograph indicating the tendency for the small oat cell to take on a more spindle shape and arrange themselves in definite bands or trabeculae.

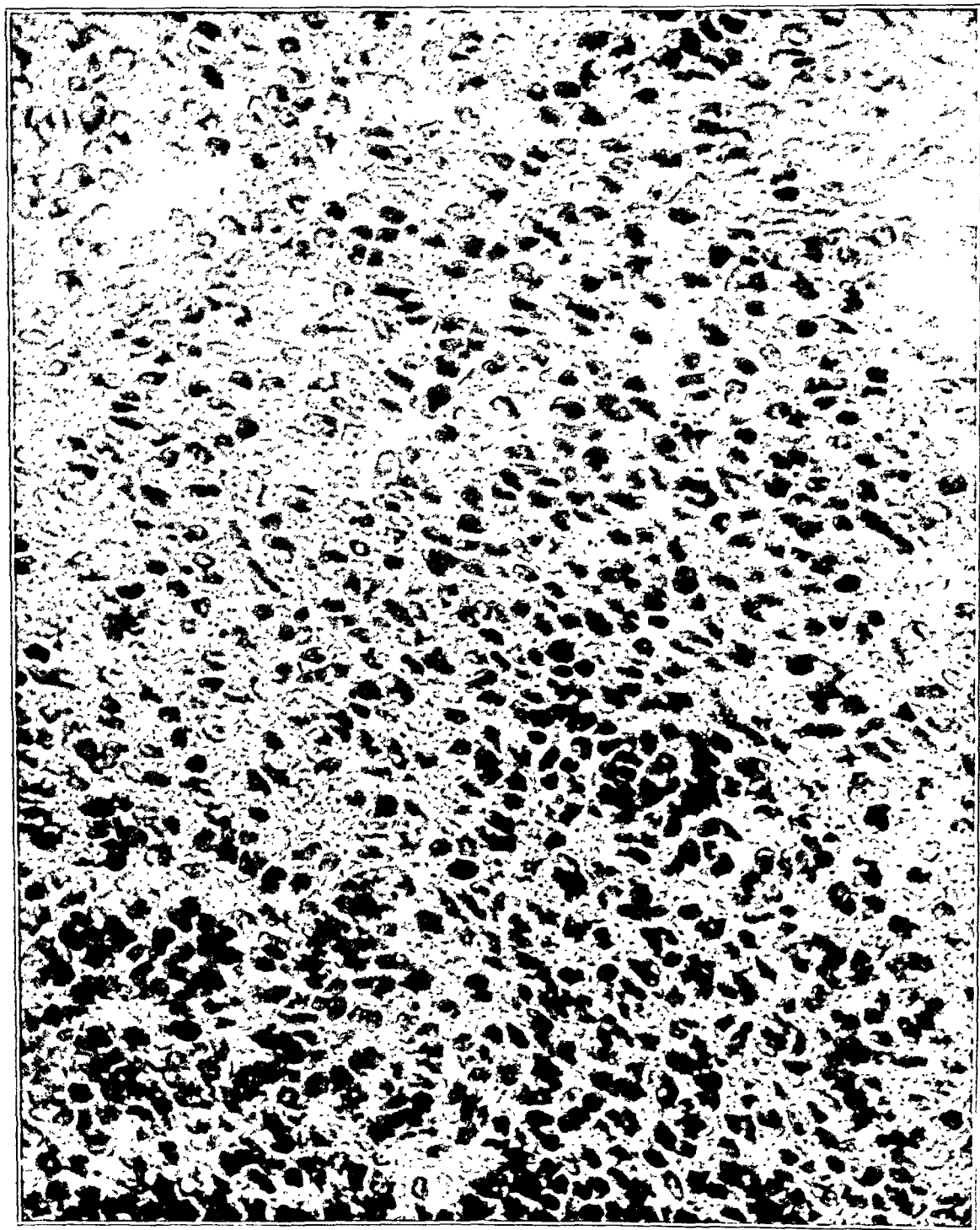


Fig. 18 (path. no. 28276).—High power photomicrograph indicating the resemblance of the tumor to small round cell sarcoma under high power.

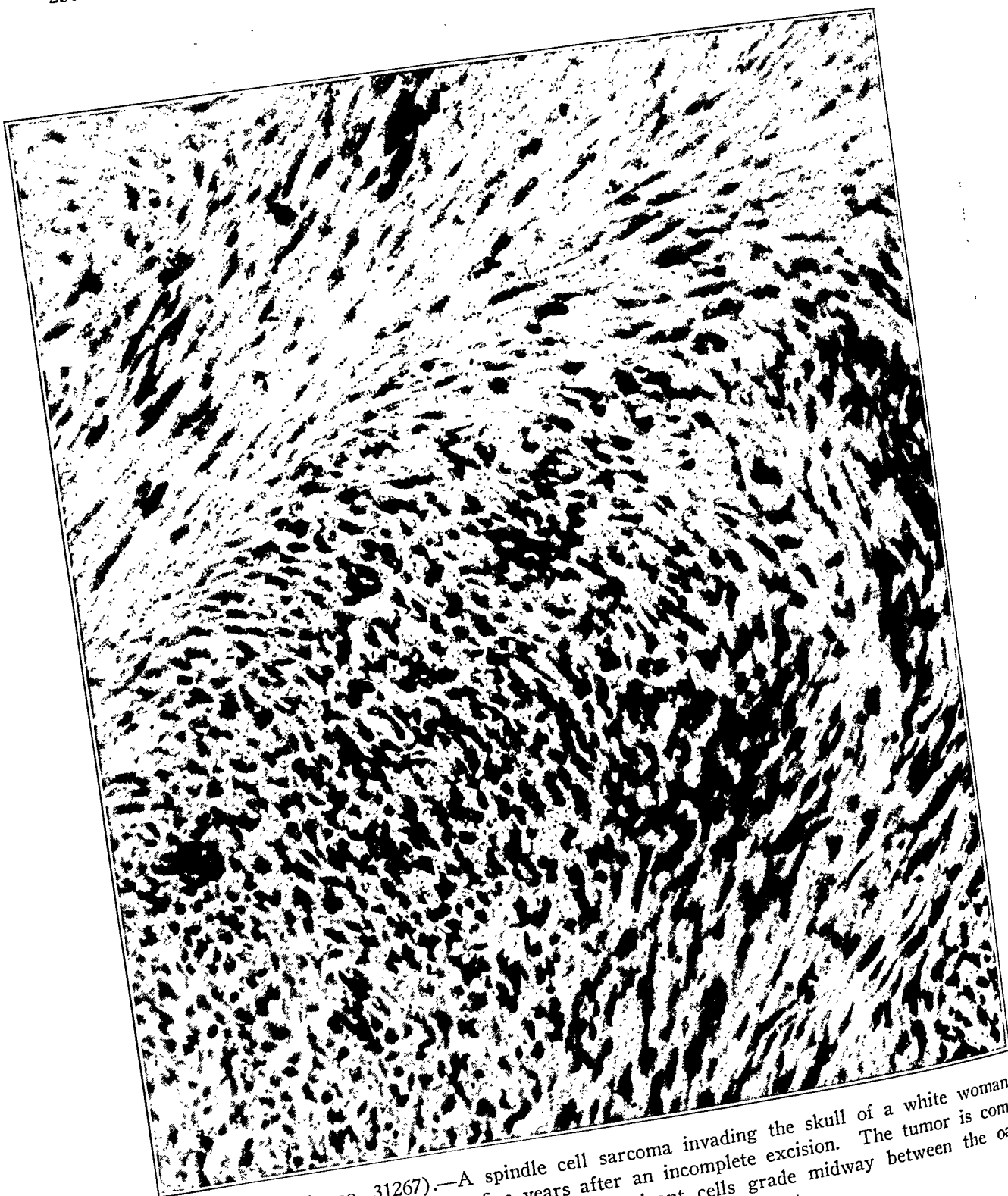


Fig. 19 (path. no. 31267).—A spindle cell sarcoma invading the skull of a white woman, aged 34, which resulted in death five years after an incomplete excision. The tumor is composed of characteristic fasciculae, and the predominant cells grade midway between the oat cell and the fibroblasts, although both of these other types are present.



Fig. 20 (path. no. 27555).—Low power photomicrograph of a fibrospindle cell sarcoma, showing the tendency for the spindle cells to assume the characteristics of fibroblasts and lay down a definite amount of intercellular collagenous material. The prognosis in this grade of fibrospindle cell sarcoma following a radical operation is extremely favorable. The tumor illustrated was from the radius of a white man, aged 49, who has remained well over seven years following amputation.



Fig. 21 (path. no. 38182).—High power photomicrograph of fibrospindle cell sarcoma, the gross specimens of which is shown in figure 10. The illustrations show the variety of cells grading from oat cells to fibroblasts included in these types of tumors. Note the tendency for the nuclei of the sarcomatous cells to assume a large vesicular form.

logic behavior and prognosis is sufficiently different to warrant setting them aside as a definite subgroup in which the grade of malignancy is extreme.

On the other hand, the more benign fibrospindle cell and fibrosarcomas in which many fibroblasts are present with an abundant

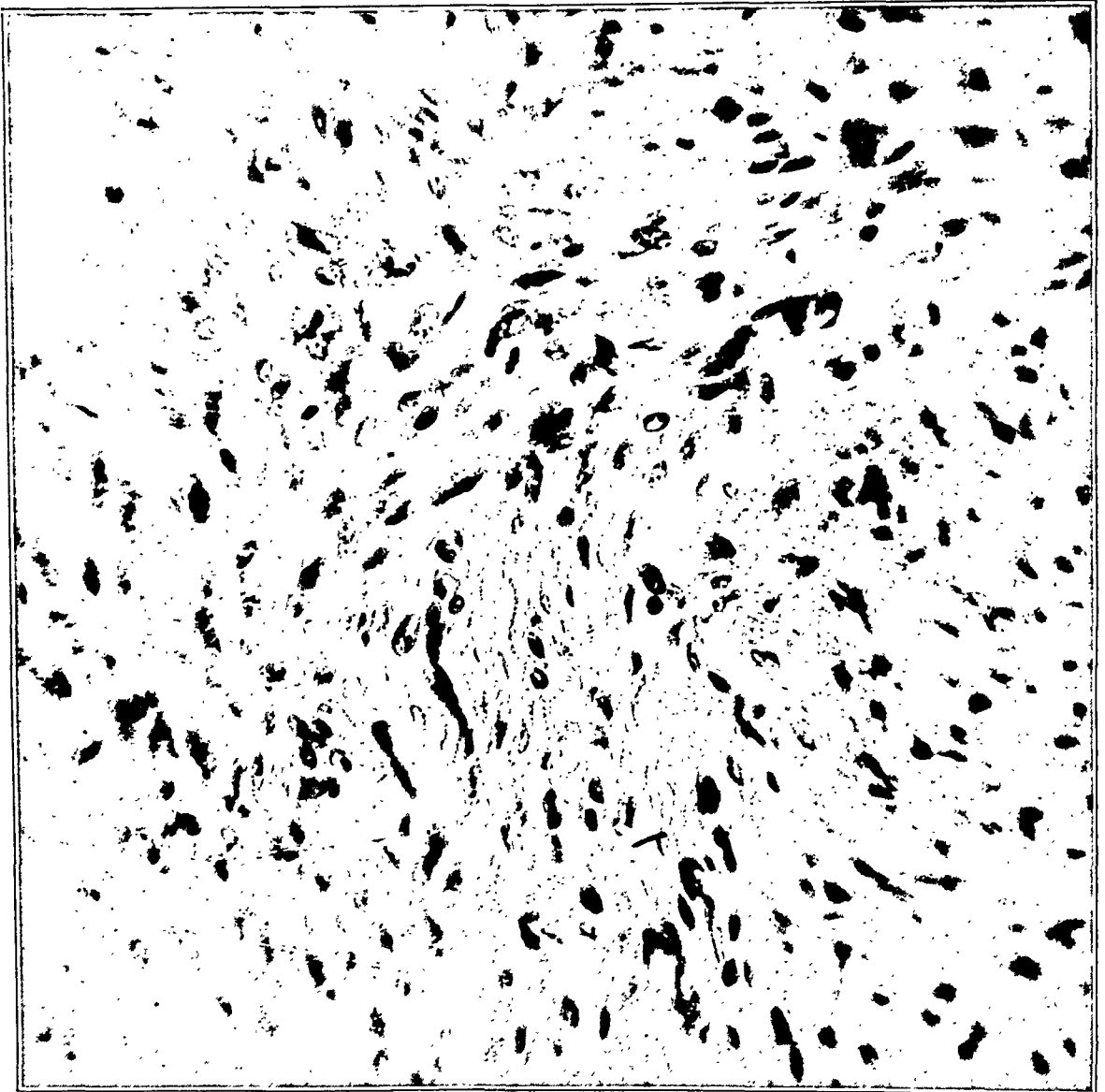


Fig. 22 (path. no. 23407).—Photomicrograph of the tumor shown in figures 6 and 13. The tumor is composed predominantly of adult fibroblasts with a conspicuous amount of collagenous intercellular substance. The nuclei are small, and the tumor is essentially a rapidly growing fibroma.

amount of intercellular substance are very slowly growing sarcomas that metastasize late despite a tendency to recur locally. They con-



Fig. 23 (path. no. 40934).—Photomicrograph taken at the margin of a cross-section of the humerus in a human embryo of 90 mm. The humerus is composed at this stage of calcified cartilage surrounded by a small rim of osteoid substance. Outside of this osteoid cuff is seen the primitive periosteum composed of oat and spindle cells or embryonic fibroblasts. The photomicrograph supports the contention that the cycle of histogenesis in fibrosarcoma is from oat cell to fibrospindle cell to fibroblast.

stitute another subgroup in which the grade of malignancy is definitely low.

In between the oat cell type and the more highly differentiated fibrospindle cell forms is the spindle cell sarcoma which merges on the one hand with the oat cell type and on the other with the fibrospindle cell series. If the cellularity in this type of tumor is marked, and if there is any resemblance to the oat cell type, it is best to be on the safe side and treat it radically in the same manner.

These various forms or grades of fibrosarcoma are to be distinguished from osteogenic sarcoma of the bone by the absence of cartilage or bone formation. Unlike the osteolytic variety of osteogenic sarcoma in which both cartilage and bone formation may be absent, the nuclei of these tumors show little or no tendency toward bizarre malignant forms, and tumor giant cells are absent (fig. 24). The presence of small giant cells of the epulis type may occur, but these are rare and are usually associated with spicules of bone undergoing necrosis.

These tumors of the fibrosarcoma group must also be distinguished microscopically from sarcoma of neurogenic origin which may secondarily invade the bone and which has quite distinct growth properties. The myxomatous substance, the elongated waving nucleus with the tendency to fibrillae formation and the enlarged tumor giant cell which are all typical of neurogenic sarcoma (fig. 31) are not characteristic of these neoplasms.

Prognosis and Treatment.—The prognosis and treatment of these tumors depends primarily on an accurate microscopic analysis, and secondarily on the degree of bone invasion and on the type of involvement of important vessels or nerves. From the microscopic standpoint, it is essential to rule out the more malignant neurogenic sarcomas and the more highly malignant osteogenic sarcomas. This is not always an easy matter, but a careful perusal of the photomicrographs included here together with the diagnostic points just mentioned will permit a fair degree of accuracy in this regard.

If the tumor is microscopically of the fibrospindle cell series, it is necessary to grade its degree of malignancy by determining whether it is of, or closely related to, the oat cell type or whether it resembles, or belongs to, the more highly differentiated fibrosarcoma group. In the present series of thirty-one cases in the fibrospindle cell series little difficulty was experienced in dividing these tumors into the undifferentiated and differentiated form (tables 1 and 2). This was done on a purely microscopic basis without knowledge or reference to the clinical results. After this microscopic grading had been carried out, the clinical features and the results of treatment were tabulated for the two separate groups, the more differentiated spindle, fibrospindle and



Fig. 24 (path. no. 27852).—High power photomicrograph of an osteolytic variety of osteogenic sarcoma showing the bizarre nuclear forms characteristic of this very malignant tumor in contradistinction to the more benign fibrospindle cell sarcoma.

fibrosarcoma tumors being placed in one group and the more malignant and undifferentiated oat cell type in the other.

Twenty-two cases were placed in the differentiated fibrospindle cell group. The ages of the patients ranged from 12 to 58 and the duration of the tumor from one to forty-eight months. None of these patients died within a period of five years after treatment, if exception is made of one patient who succumbed to tuberculous pneumonia and another on whom curettement followed by radium implantation was done. Even when adequate treatment was not given, as in case 31267 (fig. 19) in which the neoplasm invaded the skull, the duration of life reached five years. In all cases of primary amputation in which adequate follow-ups are available, the patients were cured and are living from six to twelve years after operation. When local operation was done the tumor invariably recurred, although in most instances life was prolonged beyond five years by an ultimate amputation or by further excision accompanied by deep roentgen or radium therapy. Repeated local operations, however, have never proved sufficient to cure a case, although a woman of 33 with a tumor in the region of the lower end of the femur lived for nine years before ultimately succumbing to pulmonary metastases.

The value of deep roentgen and radium therapy is difficult to establish in these cases. The tumor is not particularly radiosensitive, and after a local operation followed by roentgen therapy and radium the tumor has usually recurred. The outstanding conclusion that can be drawn is that in face of marked bone involvement a local operation is insufficient in these tumors of the fibrospindle cell group, and even local operation plus roentgen and radium therapy is usually not sufficient to prevent a recurrence. The tumor, however, is slow to metastasize and may be held in check from five to ten years by repeated local operation accompanied by roentgen or radium therapy.

Whether to combat the tumor by repeated treatment or insure its eradication by primary amputation depends on its location and the degree of bone involvement. In a vital location such as the skull, repeated excision accompanied by roentgen or radium therapy is the only procedure possible. In the extremities, if bone involvement is not marked and the cortex is still intact and if the important vessels and nerves are not included in the tumor mass, local excision may be tried if the tumor is encapsulated, and an attempt made to save the limb. The microscopic pathologic process, however, must be checked at operation to rule out the oat cell type of fibrospindle cell sarcoma and to rule out the mixed spindle and large cell sarcoma of neurogenic origin. If the local operation is done, it should be followed by deep roentgen or radium therapy. When the tumor recurs, the limb should be promptly amputated.

When bone involvement is marked and important vessels and nerves are included in the tumor mass, the function of the limb cannot be saved, and the difficulty in eradicating the tumor with the consequent danger of recurrence justifies an amputation.

When the tumor is of the undifferentiated oat cell type, neither local excision nor roentgen or radium therapy offer anything in the way of a permanent cure, and if the location of the tumor permits, primary amputation should be done. These conclusions are supported by the data shown in table 2. It will be seen that of the nine cases tabulated, permanent cure was obtained in only one (a tumor in the lower end of the humerus present in an infant at birth), and in this instance primary amputation was performed. In the case in which radium therapy was attempted it was of no avail, and even primary amputation did not suffice to establish a cure in most instances.

NEUROGENIC TUMORS INVOLVING BONE

While the connective tissue tumors of the fibrospindle cell group that invade bone may arise at variable sites in the investing fascia about such structures as bone and muscle, vessels, etc., it is possible that a group of tumors of quite different and more specific cellular composition may arise among these same structures overlying the bone and produce similar osseous involvement. Such tumors have a cellular composition that identifies them with the structure from which they arise and vary in their histology according to the tissue of origin. Among this group of tumors must be enumerated, neurogenic sarcoma, angiomas, myosarcoma and lipomas.

In the present series of cases there were fourteen tumors involving bone that could be specifically related to nerves in the vicinity. These new growths showed by the presence of wavy nuclei, fibrillae, myxomatous substance and tumor giant cells an origin from neural elements. They could also be related by microscopic appearance, clinical and pathologic behavior, to a far larger group of subcutaneous and soft part tumors of known neurogenic origin studied in this laboratory (Lewis and Hart²).

Clinically and in the roentgenogram, these neurogenic tumors (table 3) bear a close resemblance to the lesions of the fibrospindle cell series just discussed. Pathologically, also, the similarity is marked between the two groups. Like the fibrosarcomas, the neural tumors may have a marked fibrillar structure and show under the microscope many spindle cells (fig. 31). Like these fibrous growths that show a continual gradation from the benign fibroma to the most malignant spindle cell forms,

2. Lewis, Dean; and Hart, Deryl: Tumors of Peripheral Nerves, *Ann. Surg.* 92:961, 1930.

TABLE 2.—Undifferentiated Forms of Fibrospindle Cell Sarcoma

Path. No.	Race	Sex*	Age	Location	Duration, Mo.	Symptoms	Roentgenologic Picture	Treatment	Microscopic Picture	Result
38672	W	♂	25	Femur, lower	...	Pain, tumor	Osteoporosis, periosteal shadow	Explored, amputated December, 1922	Oat cell sarcoma	Living 3½ yr.
35008	W	♂	30	Tibia, upper	72	Trauma, pain, swelling, later two 6 wks.	Soft part shadow, considerable secondary bone destruction	Curettement, June, 1923; amputation, July 13, 1923	Oat cell sarcoma	Dead 5 mo. following amputation
30748	W	♀	30	Femur, upper	...	Pain, tumor	Soft part shadow, bone destruction	Excision, June, 1922	Oat and spindle cell sarcoma	Dead of tumor, no date
29691	W	♀	40	Tibia, left lower	96	Pain, tumor, trauma	Soft part shadow, slight secondary bone destruction	Exploration with cautery, amputation	Oat cell sarcoma	Dead within 16 mo. following amputation
28276	W	♀	½	Humerus, lower	6	Tumor at birth	Large soft part shadow, advanced secondary bone destruction	Excision, amputation, June 8, 1920	Oat cell sarcoma	Well 9 yr., 11 mo. following amputation
26404	W	♂	..	Sacrum	...	Trauma, pain and tumor	Excision, radium	Oat cell sarcoma	Dead 6 mo. following injury
24520	W	♂	..	Pelvis	...	Tumor	Resection of hip joint May 10, 1919	Oat cell sarcoma	Dead 2 yr. later
13350	W	♀	69	Humerus, lower	108	Fracture, subsequent swelling, pain, limitation of motion	Amputation, Oct. 22, 1912	Oat cell sarcoma	Dead 2 yr., 1 mo. later
7583	W	♂	40	Femur, lower	12	Trauma, pain, tumor	Amputation, Sept. 29, 1906	Oat cell sarcoma	Dead 6 mo. later

* ♀ indicates female, ♂ male.

there is also a gradual transition among the neural tumors from the benign neurinomas to the most malignant forms of neurogenic sarcoma.

Unfortunately for the treatment of sarcoma in general, and particularly for the forms of sarcoma most frequently localized in the extremities, the pathologic distinction between tumors of the fibrospindle cell series and tumors of the neurogenic series is not frequently made. Nor, in most instances, is the pathologist familiar with the variations in the histologic picture that accompany the gradations from the more benign fibromas to the more malignant oat cell sarcomas in contrast to the transitions that accompany the gradations between the more benign neurinomas and the more malignant neurogenic sarcomas. As a result, much confusion has arisen in the literature in regard to the diagnosis and prognosis of these growths and in regard to the proper forms of treatment.

In those neurogenic tumors that invade the bone, the more malignant and cellular forms predominate, and in no instance of this series was there any difficulty in setting the tumor apart as a sarcoma as opposed to a benign neurinoma. This cellular sarcoma structure is in keeping with the invasive character of the growth which has forced its way into the osseous substance. While thus easily distinguished from the benign neurinomas, careful microscopic study was necessary to delineate these growths from fibrospindle cell sarcoma. However, that the microscopic distinction was accurately made is borne out by the clinical features and results of treatment. The clinical follow-ups show that once a neurogenic sarcoma has invaded the bone the chances for cure, no matter how radical the mode of treatment, are practically nil.

Clinical Features.—While the most important points of distinction are not clinical or roentgenologic but relate to the pathologic process and to the response of the neurogenic tumors to treatment, these neoplasms nevertheless present definite clinical peculiarities. The age of the patient is usually well over 30 (from 32 to 75), and the duration of clinical symptoms averages over one year. In only one case of neurogenic sarcoma involving the bone in this series was a child affected. This was in a white boy of 7, who had a tumor in the soft parts of the buttocks (fig. 25), and in this instance, the osseous involvement differed from that in the other cases in that the extension to the bone which involved the skull and the vertebra was due to metastases to these regions.

The bone involvement as shown in the roentgenogram (figs. 26, 27, and 28) is more pronounced in those instances due to neurogenic sarcoma than in the cases caused by fibrospindle cell sarcoma. Pathologic fracture may occur (fig. 26), and the lesion may resemble metastatic

TABLE 3.—*Neurogenic Sarcoma Involving Bone*

Path. No.	Race	Sex*	Age	Location	Duration, Mo.	Symptoms	Röntgenologic Picture	Treatment	Microscopic Picture	Result
43742	W	♀	37	Tibia, upper	12	Pain, swelling	Soft part shadow, roughening of bone	Röntgen therapy, complete excision, December, 1930	Neurogenic
43482	W	♂	38	Tibia, upper	72	Pain, swelling	Soft part shadow, large area of bone destruction	Amputation, August, 1930	Neurogenic
38722	W	♂	73	Fibula, upper	24	Pain, tumor	Curettement, December, 1926; radium, postoperative x-ray	Neurogenic
38304	W	♀	37	Fibula	12	Pain along distribution of nerve, swelling	Soft part tumor, bone erosion	Refused treatment
36721	W	♂	75	Femur, lower	..	Pain, tumor	Amputation, Jan. 29, 1925	Neurogenic	Dead 7 mo. later
35248	W	♀	16	Tibia, upper	Soft part shadow, secondary bone destruction	Amputation, Oct. 21, 1924; pre-operative x-ray, Feb. 23, 1924	Neurogenic	Well 5 yr. and 7 mo.
34628	W	♂	44	Ischium and groin	2	Pain, swelling	Bone erosion	Radiation (radium); excision, May, 1921	Neurogenic	Dead 11 mo. later
33928	W	♂	46	Femur, lower	4	Pain, pathologic fracture	Soft part shadow, extensive bone destruction	Exploration; Sept. 11, 1923; x-ray, amputation, Sept. 23, 1923	Neurogenic	Dead 14 mo. later
30555	W	♂	7	Buttocks, skull	1	Pain, swelling	Bone destruction in skull	Exploration, Dec. 12, 1921; radium, January, 1922	Neurogenic	Dead 2 yr. later; metastasis plural; extension of tumor through dura to brain; skull and thoracic vertebrae involved with tumor
27822	W	♂	77	Femur, lower	10	Pain, tumors	Soft part shadow, advanced secondary bone destruction	Neurogenic	Well over 1 yr.
26593	W	♂	77	Femur, lower	10	Pain, tumors	Soft part shadow, advanced secondary bone destruction	Neurogenic	Dead 2 yr. later
26178	W	♂	32	Femur, lower	12	Pain, tumor four months	Soft part shadow, secondary bone destruction	Resection, May 29, 1920; bone graft	Neurogenic	Dead 7½ mo. following operation
25888	W	♂	37	Femur, lower	5	Tumor, pain, pulsation	Soft part shadow, complete secondary destruction of upper end of radius	Irradiation, March, 1920	Neurogenic	Dead 2 mo. later
17671	W	♀	65	Radius, upper	6	Pain, tumor	Soft part shadow, complete secondary destruction of upper end of radius	Amputation, June 12, 1915	Neurogenic	Dead 6 mo. following operation

* ♀ Indicates female, ♂ male.

carcinoma or osteolytic sarcoma of central origin. In other respects the roentgenogram bears a remarkable resemblance to those seen in fibrosarcoma of bone. The unique changes in the length and structure of the bone which may be brought about by the benign types of von Recklinghausen's neurofibromatosis are not included in this study.

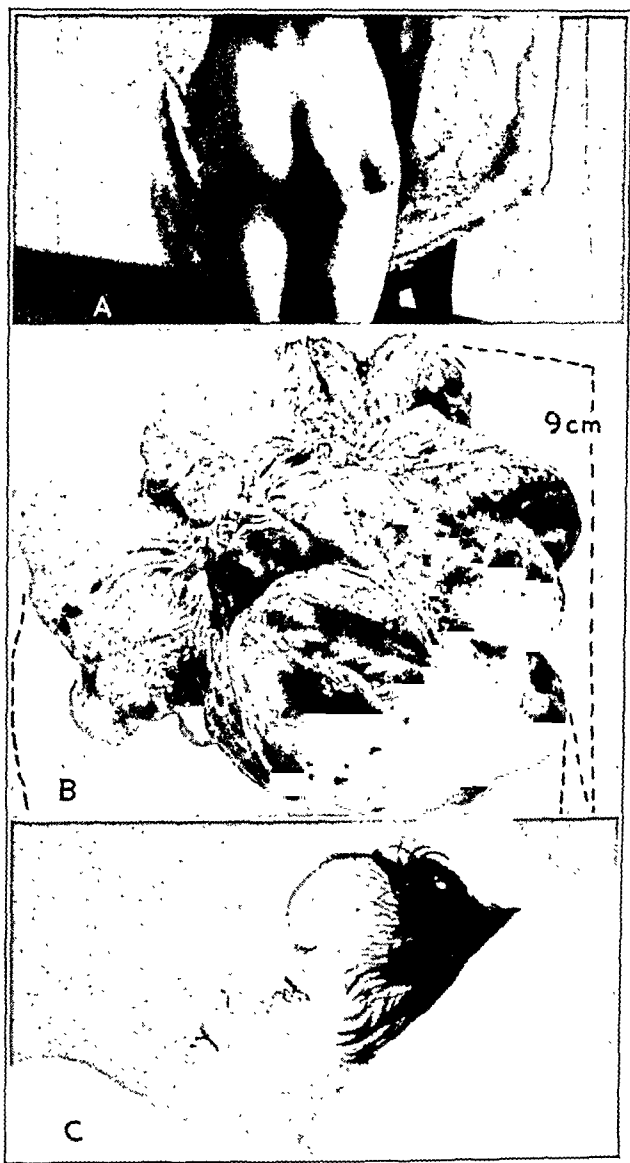


Fig. 25 (path. no. 30855).—A case of neurogenic sarcoma arising in the soft part of the buttocks of a white boy, aged 7, and invading the bone. *A* shows the original tumor which was removed by excision; *B*, the gross specimen after removal. Note the lobulated character of the growth and its gelatinous mucoid appearance. *C* shows the metastasis to the frontal bone, which invaded the dura and penetrated into the brain substance. The vertebrae were also involved by metastases. The patient died two years after the initial operation despite radium treatments.

Symptoms referable to nerve involvement, such as tingling or pain along the distribution of the nerve trunk, were not marked in this group, and once the tumor developed to an appreciable size the disturbances referable to the bone involvement dominated the clinical picture.

Pathology.—Grossly, these neurogenic tumors are less firm and more fleshy than fibrospindle cell sarcoma. They have either a soft and beefy red appearance or are composed of a gray translucent jelly-like myxom-

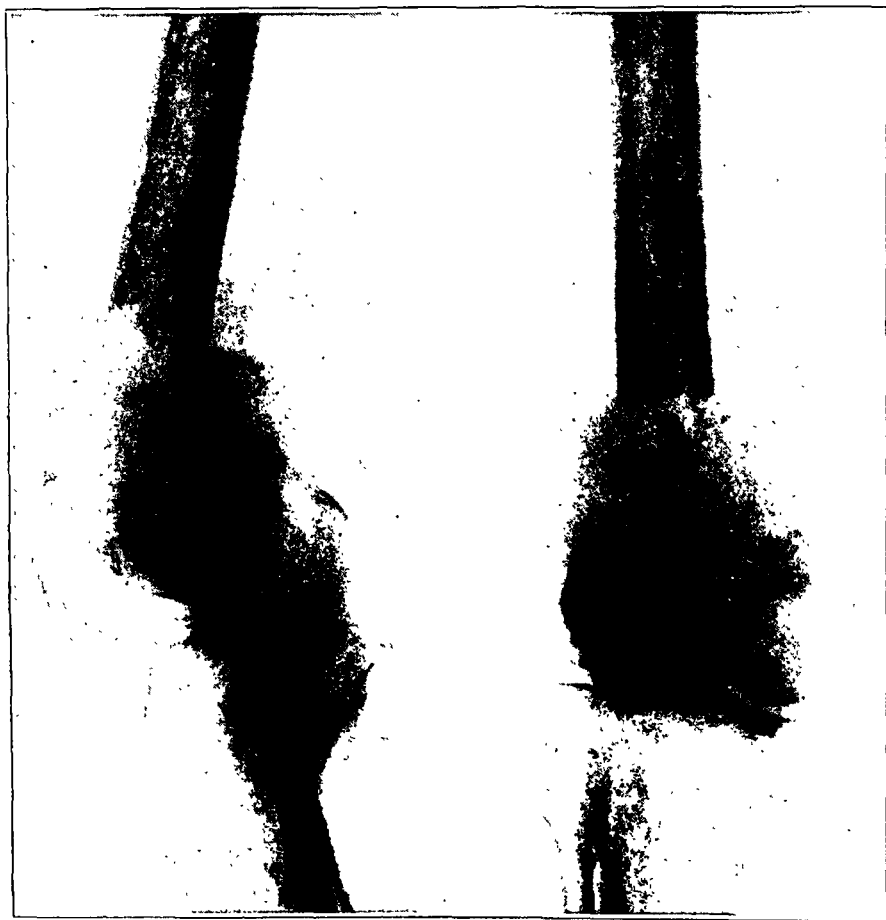


Fig. 26 (path. no. 33928).—Roentgenogram of neurogenic sarcoma occurring in a white man, aged 26, who died fourteen months following amputation. The lateral view shows well the soft part tumor invading the popliteal space. Opposite this point the entire osseous substance of the femur had been destroyed and a pathologic fracture has occurred.

atous substance. The fleshy tumor, besides finding its way into the bone, is locally disseminated along the neighboring nerve trunk, and this structure shows a decided tendency to be diffusely involved by multiple discrete or lobulated tumors of this character (fig. 20 *B*). When the marrow cavity of the bone is invaded, the white translucent areas of tumor infiltration are accompanied by neighboring regions in which

hemorrhagic and honey-combed cavities are opened up in the cancellous bone (fig. 30). The periosteum is raised by the tumor growth, and the joint cavity in the vicinity may be involved (fig. 29), a complication rare in osteogenic sarcoma but occurring in fibrosarcoma affecting bones.

Under the microscope, strands of tightly packed elongated spindle cells are very common and give these tumors a superficial resemblance to the fibrospindle cell sarcoma (fig. 31). There is, however, a faintly staining myxomatous substance that is present in fairly conspicuous areas



Fig. 27 (path. no. 26593).—Roentgenogram showing a neurogenic sarcoma which is invading the femur from without. There is a soft part shadow just above the lateral femoral condyle, and opposite this point, the cortical and cancellous bone is being destroyed by direct invasion. The patient died with pulmonary metastases, two years after amputation. For microscopic structure see figure 32.

interspersed among the spindle cell bundles. Within these myxomatous areas are found degenerating cells with small nuclei and a large faintly staining amount of rounded cytoplasm (fig. 33). The elongated spindle cell areas also present definite peculiarities. The nuclei are generally longer and more deeply staining than those found in fibrospindle cell

sarcoma and are more often rippled or waved (fig. 32). The appearance of large tumor giant cells in the section among these spindle cell areas and the tendency for the cells to line up in parallel rows are important diagnostic points, the one indicating a high degree of malignancy and the other recalling the fibrillated structure of peripheral nerves (figs. 34 and 35).

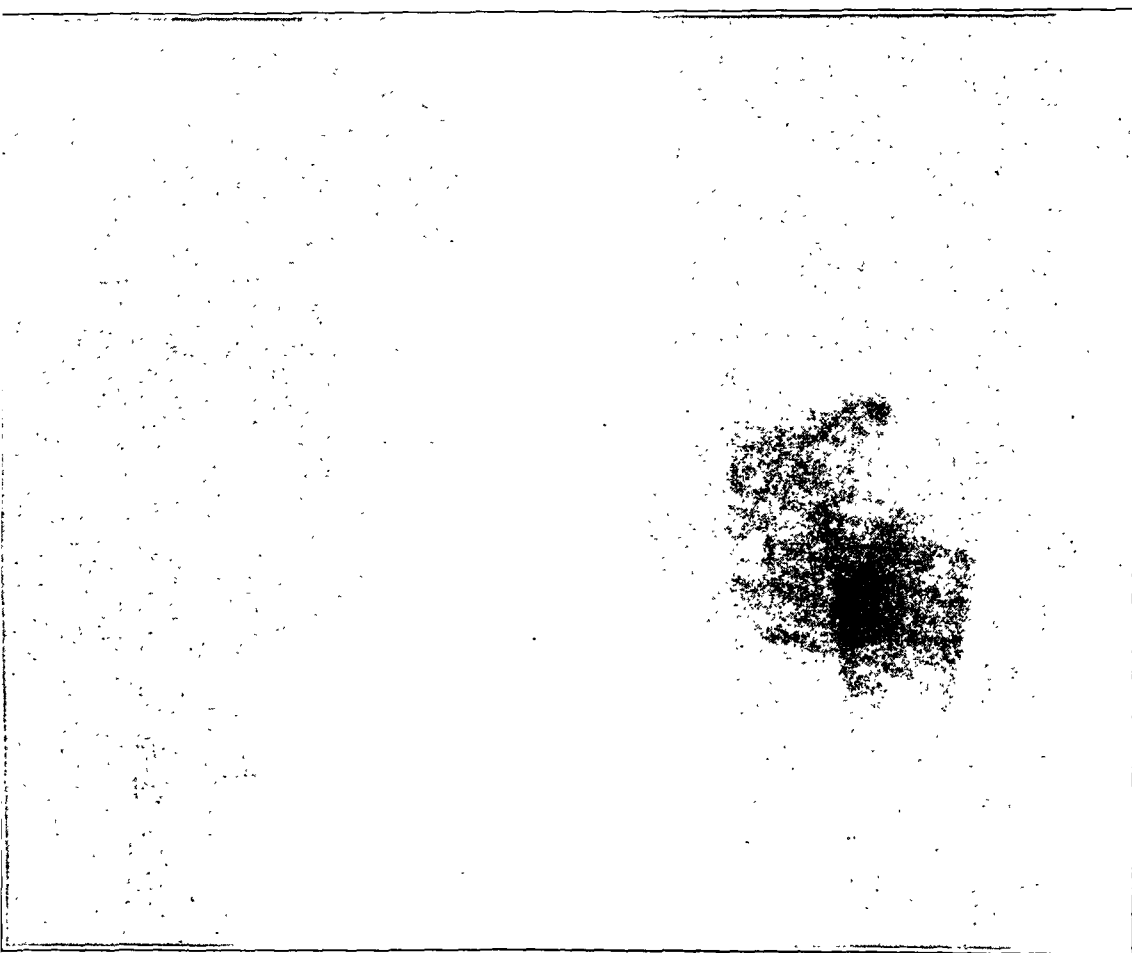


Fig. 28 (path. no. 43482).—Roentgenogram of a neurogenic sarcoma invading the outer condyle of the upper end of the tibia. Note the opaque large soft part shadow. This tumor invaded the knee joint (fig. 29).

Like fibrospindle cell sarcoma, these neurogenic tumors may be definitely graded with the microscope. Frequent myxomatous areas about which clumps of elongated nuclei in cells of the neurilemma type are found in a palisade arrangement are more typical of a benign neurinoma and are more prominent in the neurosarcomas with a slower rate of growth. So are the so-called reticular areas in which cells with small nuclei are loosely scattered (figs. 36, 37 and 38). As the tumor gives

evidence of a high degree of malignancy, large pleomorphic nuclei become scattered through the tissue and the spindle shaped cells become more tightly packed. In the highly malignant cases, tightly packed spindle cells with sharply pointed nuclei crowd out the myxomatous areas, and the tumor giant cells take on a bizarre appearance.

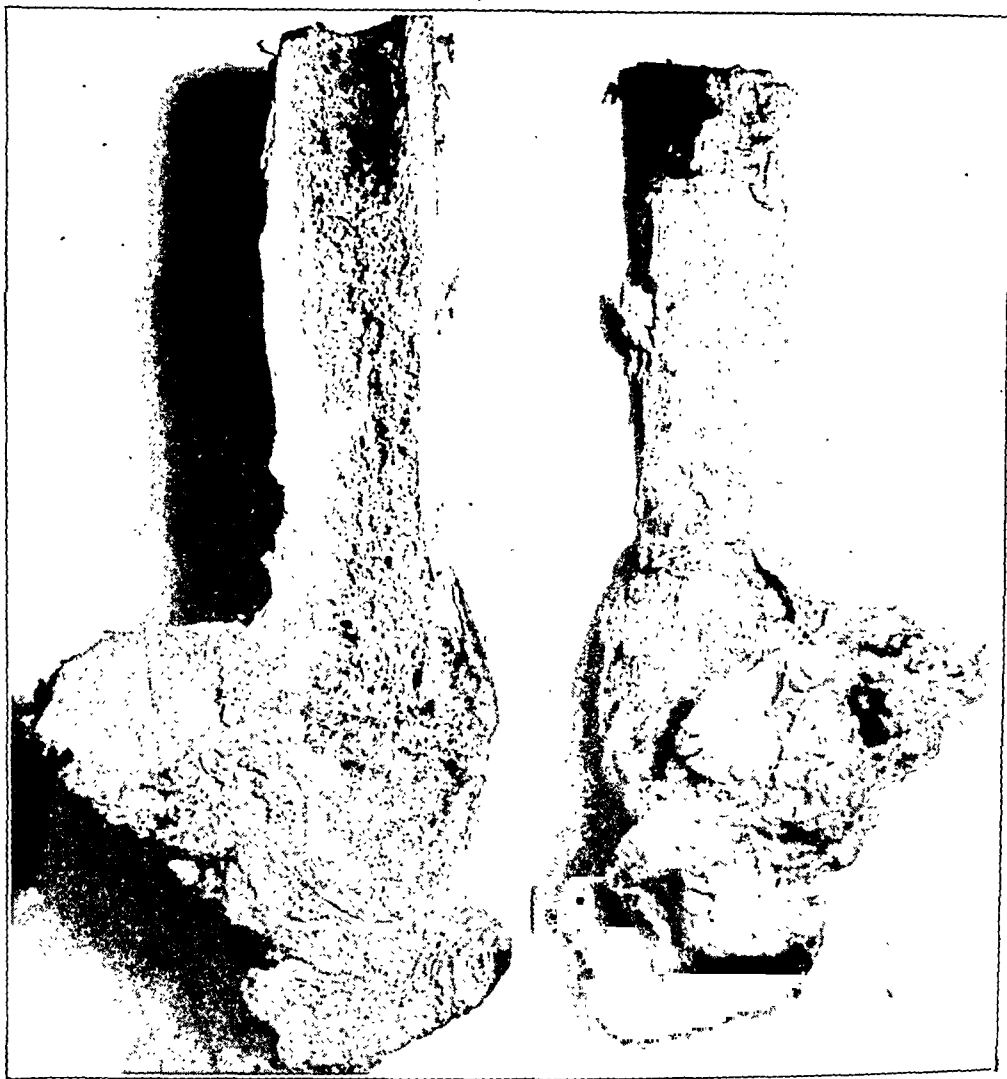


Fig. 29 (path. no. 43482).—Gross specimen of the case shown in figure 28. The specimen includes the tumor mass in the knee joint which is shown attached to and invading the lower end of the femur. The original tumor arose opposite the head of the tibia (for microscopic structure see fig. 35).

Prognosis and Treatment.—The prognosis for life in cases of neurogenic sarcoma, even after a primary amputation, is not good. These neoplasms, arising from the deep lying nerves and invading the bone, recur promptly after local operation and are not radiosensitive. Once osseous invasion has taken place, primary amputation following biopsy is the treatment of choice. There is only one cure extending over five

years in this series and this was in a young patient with a tumor invading the upper end of the tibia who was treated by amputation following a preoperative course of deep roentgen therapy. Microscopically, also, this tumor was an exception, being largely neurinomatous (fig. 36). The other eight patients who were satisfactorily traced by the follow-ups died within two years of the date of treatment, despite the fact that amputation or radical resection was done in six instances. Irradiation

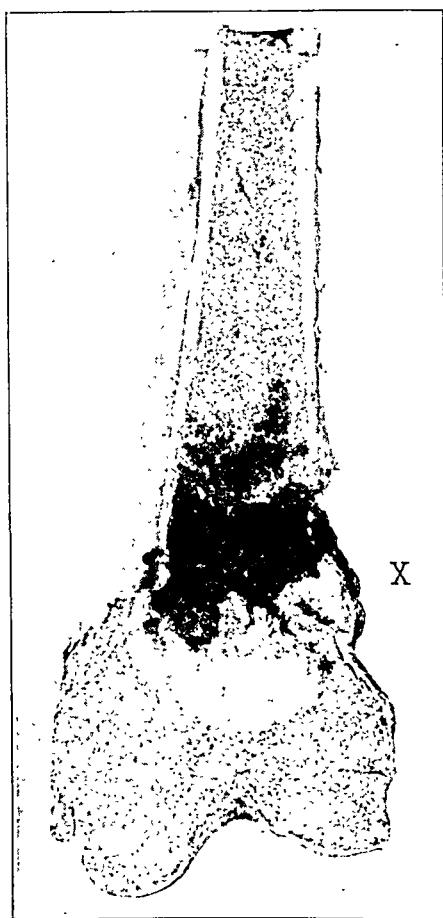


Fig. 30 (path. no. 26593).—Gross specimen of the case shown in figure 27. The tumor has gained entrance into the marrow cavity through the eroded cortex at the site marked X. A portion of the tumor infiltrating toward the epiphysis is of a white myxomatous character, while above hemorrhagic spaces have been opened up in cancellous bone.

with x-rays or radium was used in three of these fatal cases. When local operation was performed, the tumor recurred promptly, and in one instance (fig. 39) in which operation was not performed because of suspected pulmonary involvement by tumor metastases, death followed within two months, although the patient had symptoms referable to the bone involved for only five months previous to examination.

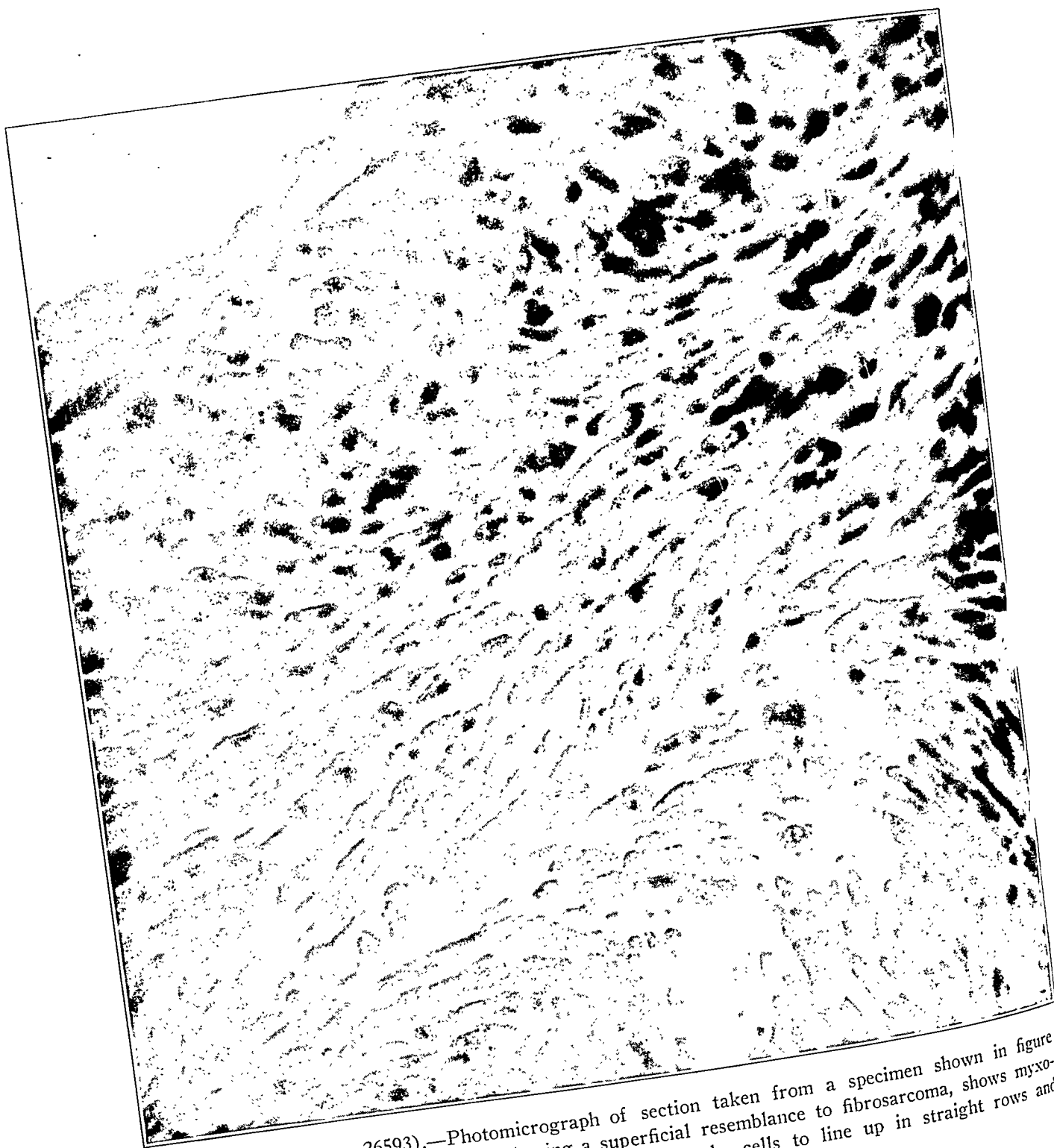


Fig. 31 (path. no. 26593).—Photomicrograph of section taken from a specimen shown in figure 30. This neurogenic tumor, although having a superficial resemblance to fibrosarcoma, shows myxomatous areas (lower right hand corner), a tendency for the cells to line up in straight rows and tumor giant cells.

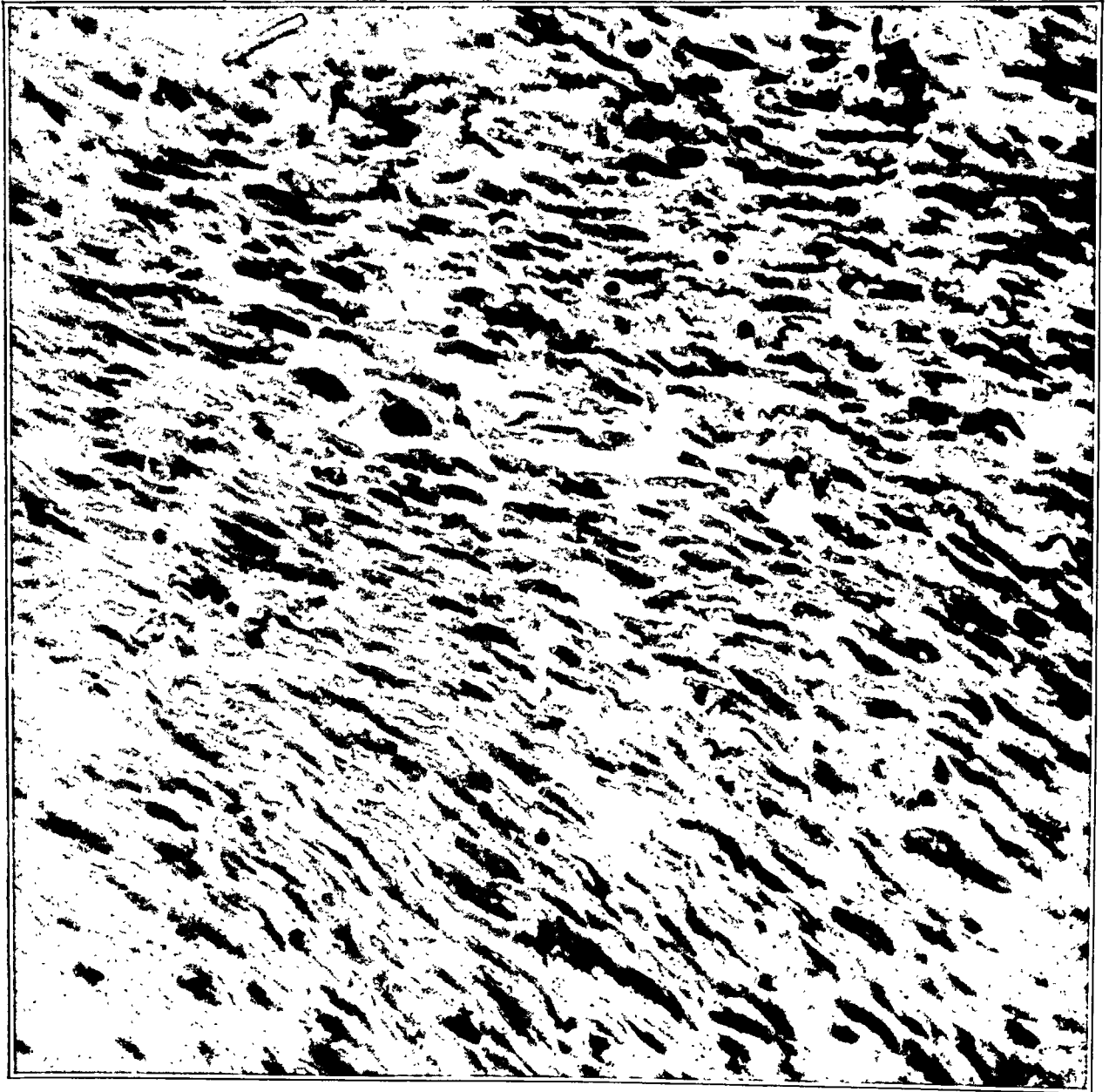


Fig. 32 (path. no. 26593).—Photomicrograph of another section from the specimen shown in figure 30. In this area, in addition to the tumor giant cells, the nuclei have a wavy or rippled appearance, characteristic of neurogenic sarcoma. There is a definite formation of fibrillae and a very scanty amount of intercellular substance. Again the cells are lining up in definite rows.

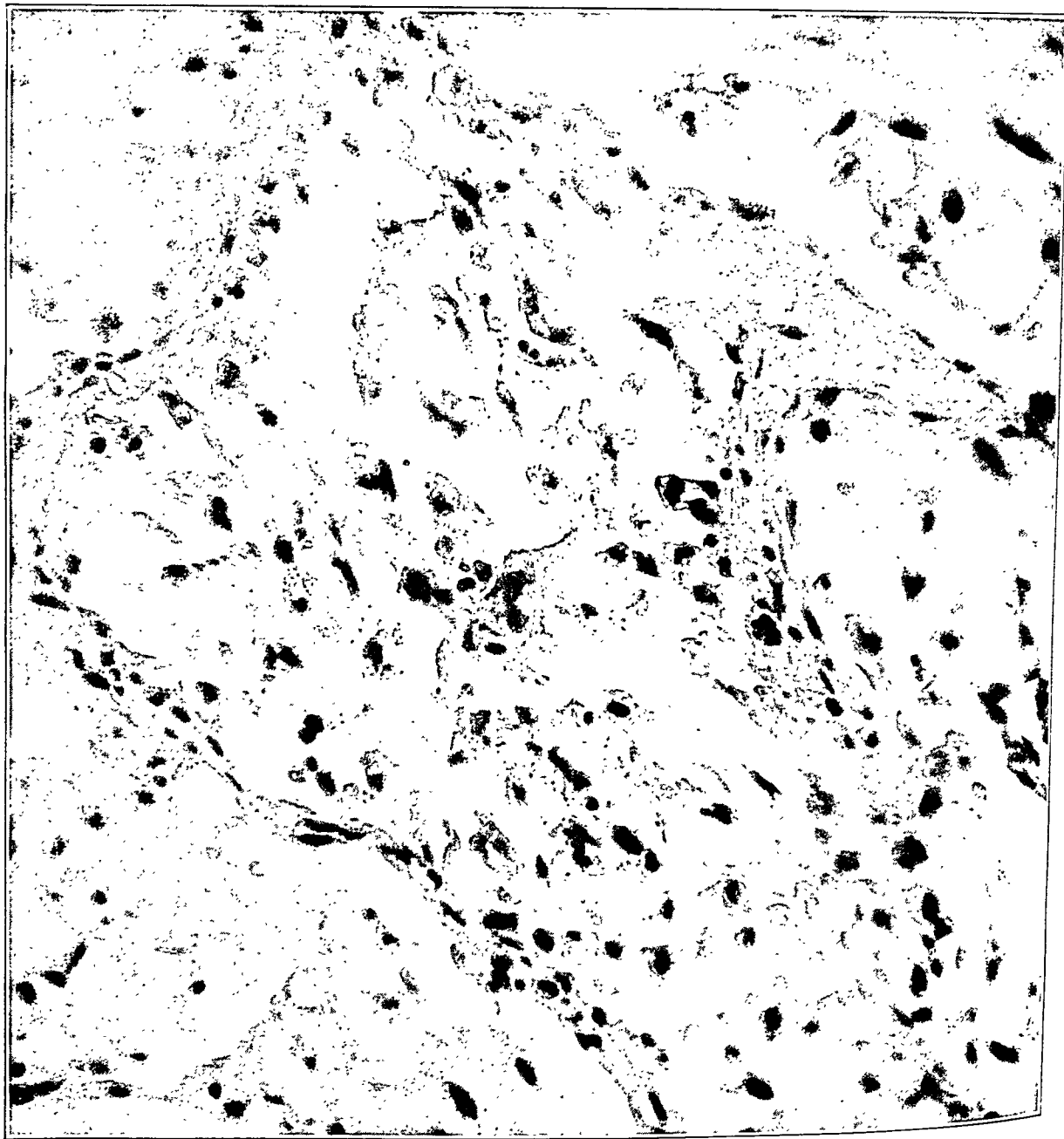


Fig. 33 (path. no. 36721).—Photomicrograph showing myxomatous areas of a neurogenic sarcoma. The patient was a white man, aged 75. The tumor occupied the popliteal space. It invaded the muscles and fascia, destroyed the femoral shaft, involved the external condyle and was beginning to invade the upper end of the tibia. The cavities in the bone were filled with a gray translucent material, typical of neurogenic sarcoma. The patient died seven months after amputation.

While the present series is too small to permit unequivocal conclusions in regard to therapy, the results observed are in accord with a far larger series of cases of neurogenic sarcoma of the same pathologic type, which occurred in the soft parts without osseous involvement. From

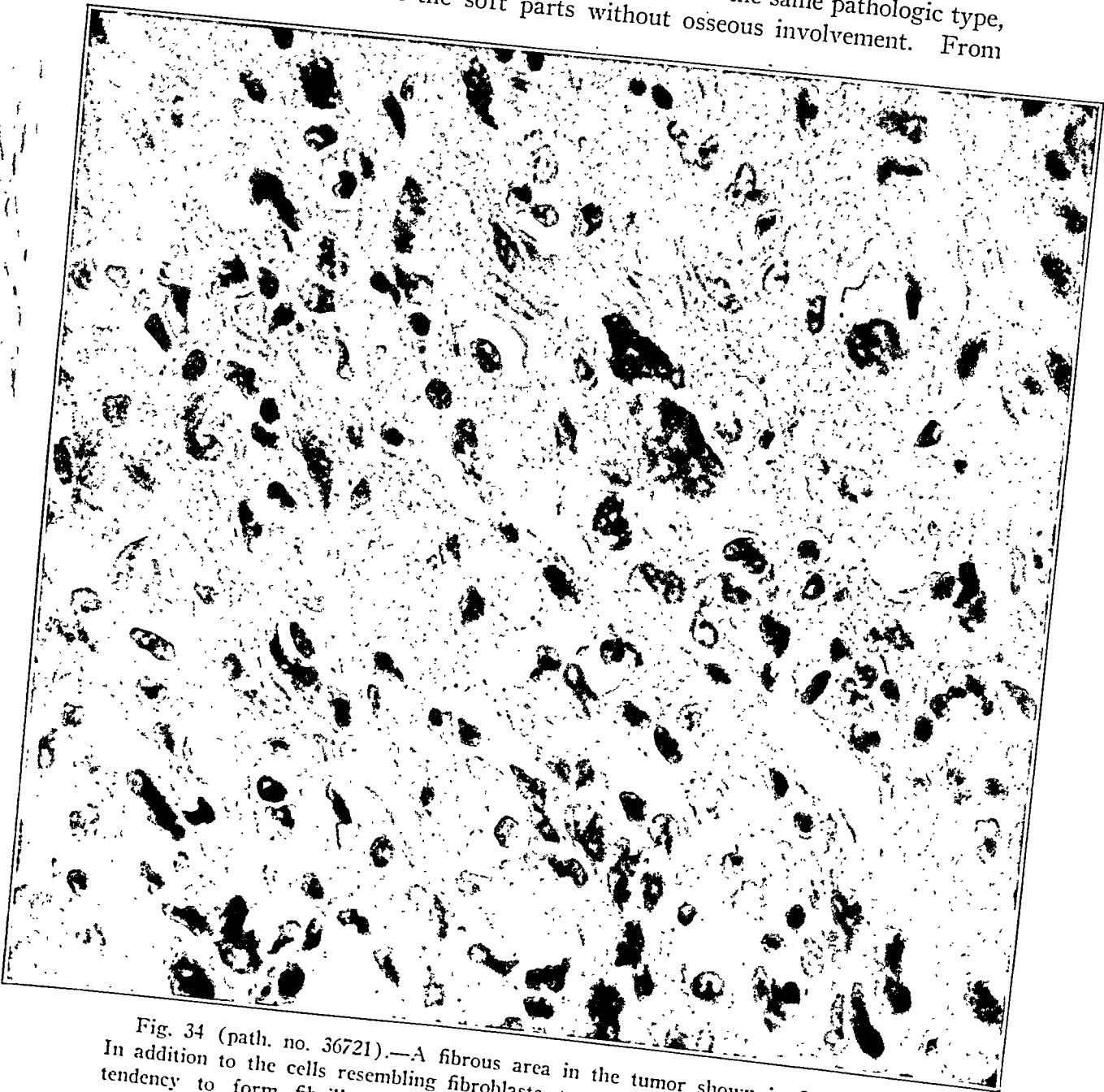


Fig. 34 (path. no. 36721).—A fibrous area in the tumor shown in figure 33. In addition to the cells resembling fibroblasts, tumor giant cells are present. A tendency to form fibrillae and areas of reticulation (typical of neurogenic sarcoma) are seen.

these combined studies it can be said that the cellular forms of neurogenic sarcoma are rarely cured, either by extensive local operation or by

irradiation with deep roentgen rays or radium. The best results are achieved by early primary amputation, and even with this radical form of treatment permanent cures are not numerous.

This gloomy outlook in neurogenic sarcoma involving bone is in marked contrast to the results obtained in the group of fibrosarcomas described in the first part of this paper. In this less malignant group it will be recalled that cures extending beyond five years were the rule,

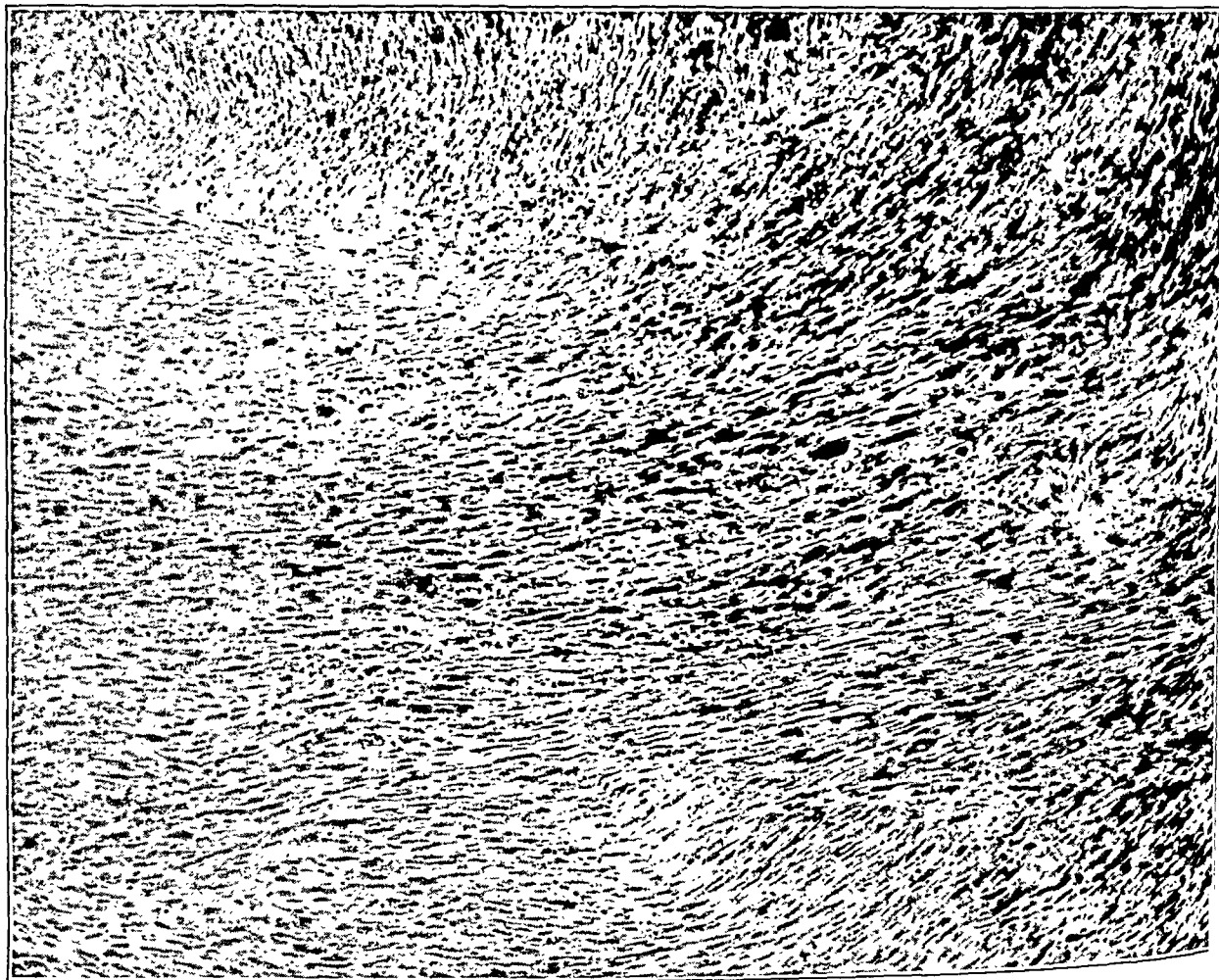


Fig. 35 (path. no. 43482).—Photomicrograph of the tumor shown in figures 28 and 29. The photograph shows well the presence of myxomatous areas, the alinement of the cells in definite rows and the large anaplastic nuclei, typical of neurogenic sarcoma.

even after the late amputation following initial recurrence. The contrast in the results between these two otherwise similar groups of tumors emphasizes the importance of distinguishing between them. Heretofore all of these neoplasms invading the bone from without by direct extension have either been loosely classed as parosteal fibrosarcoma or confused with primary sarcoma of the bone. In fact, most of the cases

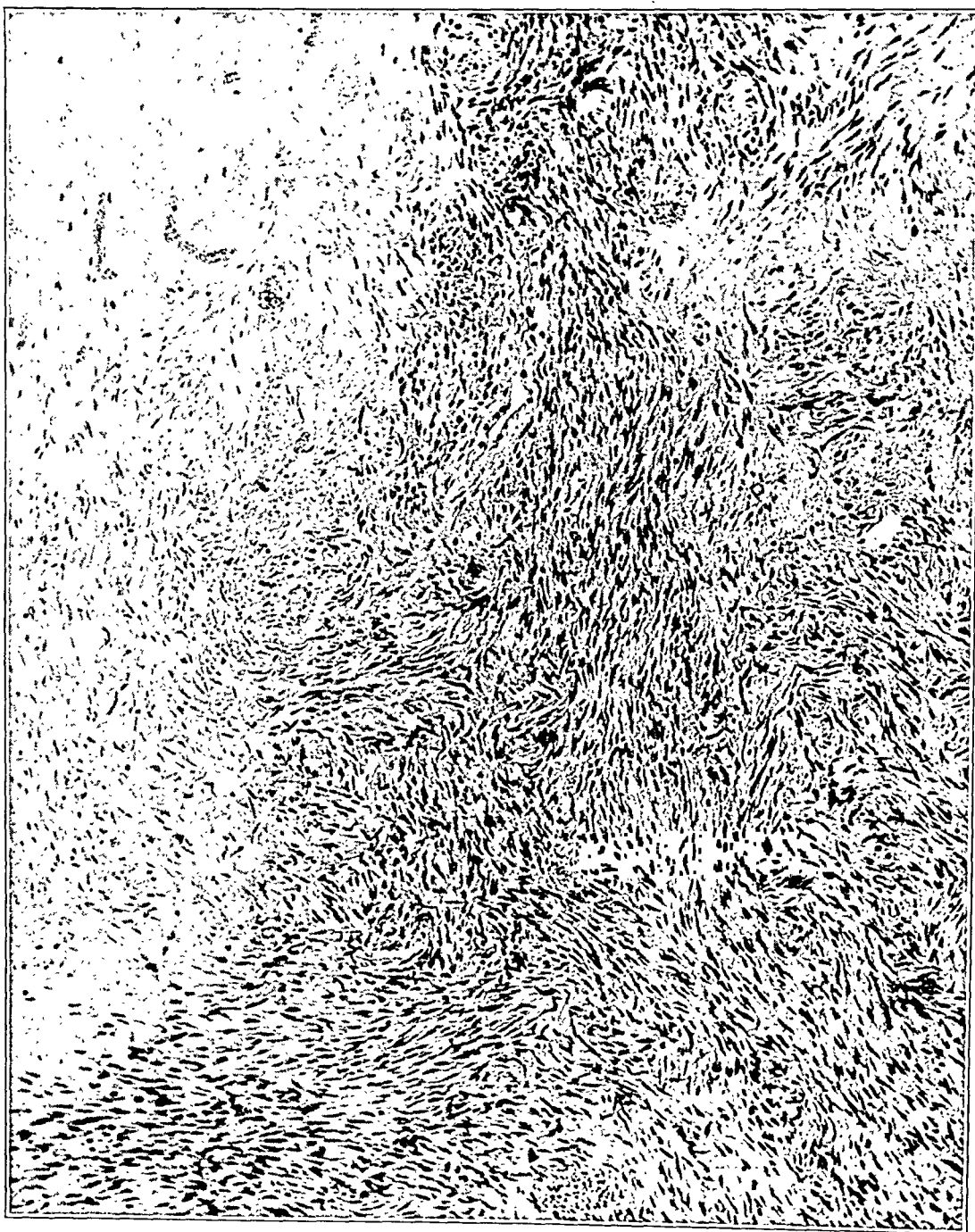


Fig. 36 (path. no. 35248).—Transitions in neurogenic sarcoma from the more benign neurinomatous type of malignancy to the more malignant forms. The early malignant change in the neurinoma is shown. Myxomatous tissue predominates, and the nuclei have a palisade arrangement.

reported here were originally diagnosed from the clinical and pathologic standpoint as primary sarcoma of the bone. It is important to bear in mind that these tumors of nonosseous origin that invade bone by direct

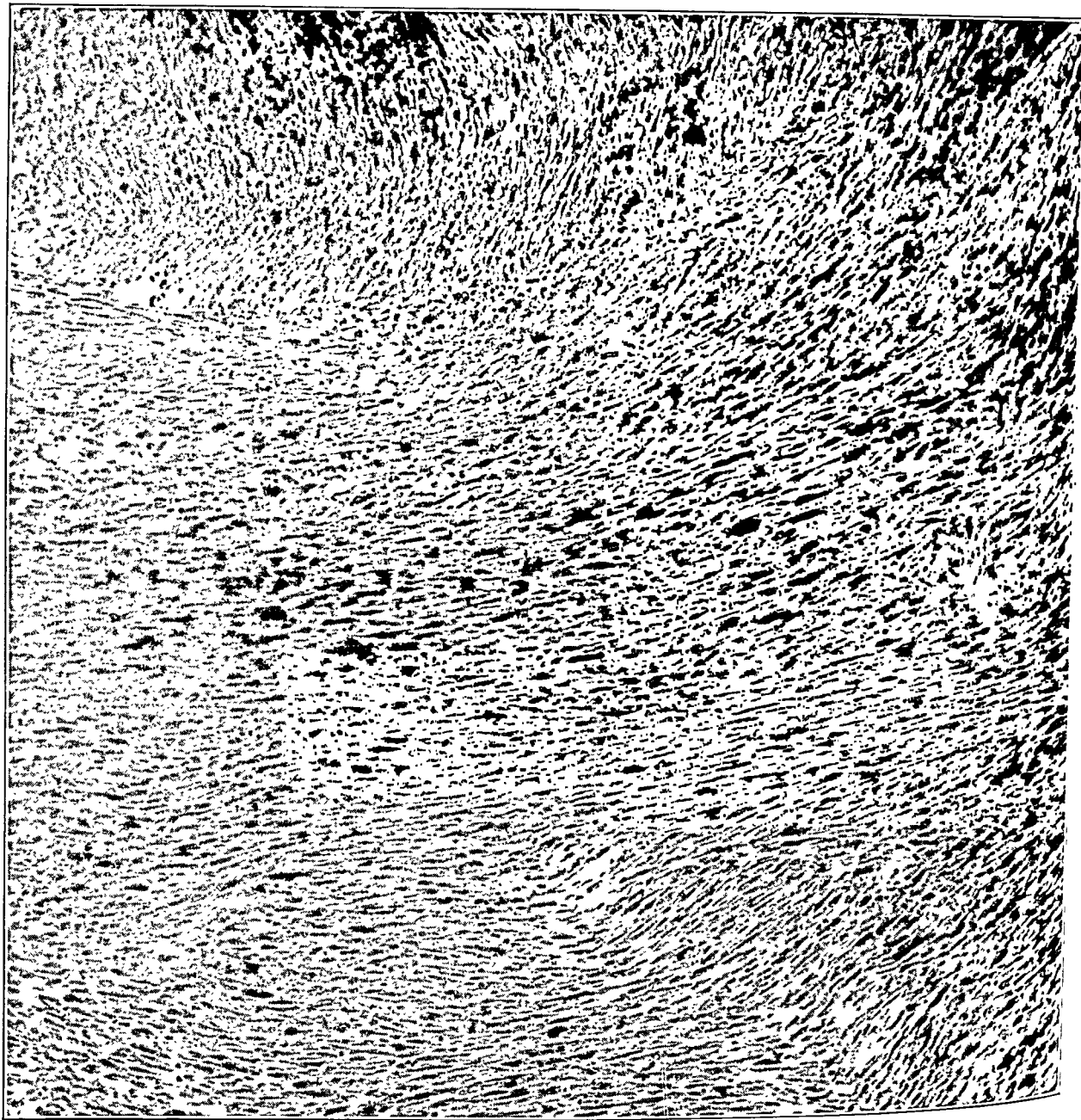


Fig. 37 (path. no. 43482).—Photomicrograph of a more malignant neurogenic sarcoma showing crowding of the nuclei, anaplastic large nuclear forms, and scarcity of intercellular substance.

extension have a variable pathologic process. When in the fibrosarcoma group and not of the oat cell type, the outlook for a permanent cure with proper treatment is exceedingly favorable if not certain (88

per cent of the patients are living after five years). When the neoplasm is of the neurogenic sarcoma type and involves the bone, the outlook is practically hopeless if the lesion is of a very cellular type, and even if the

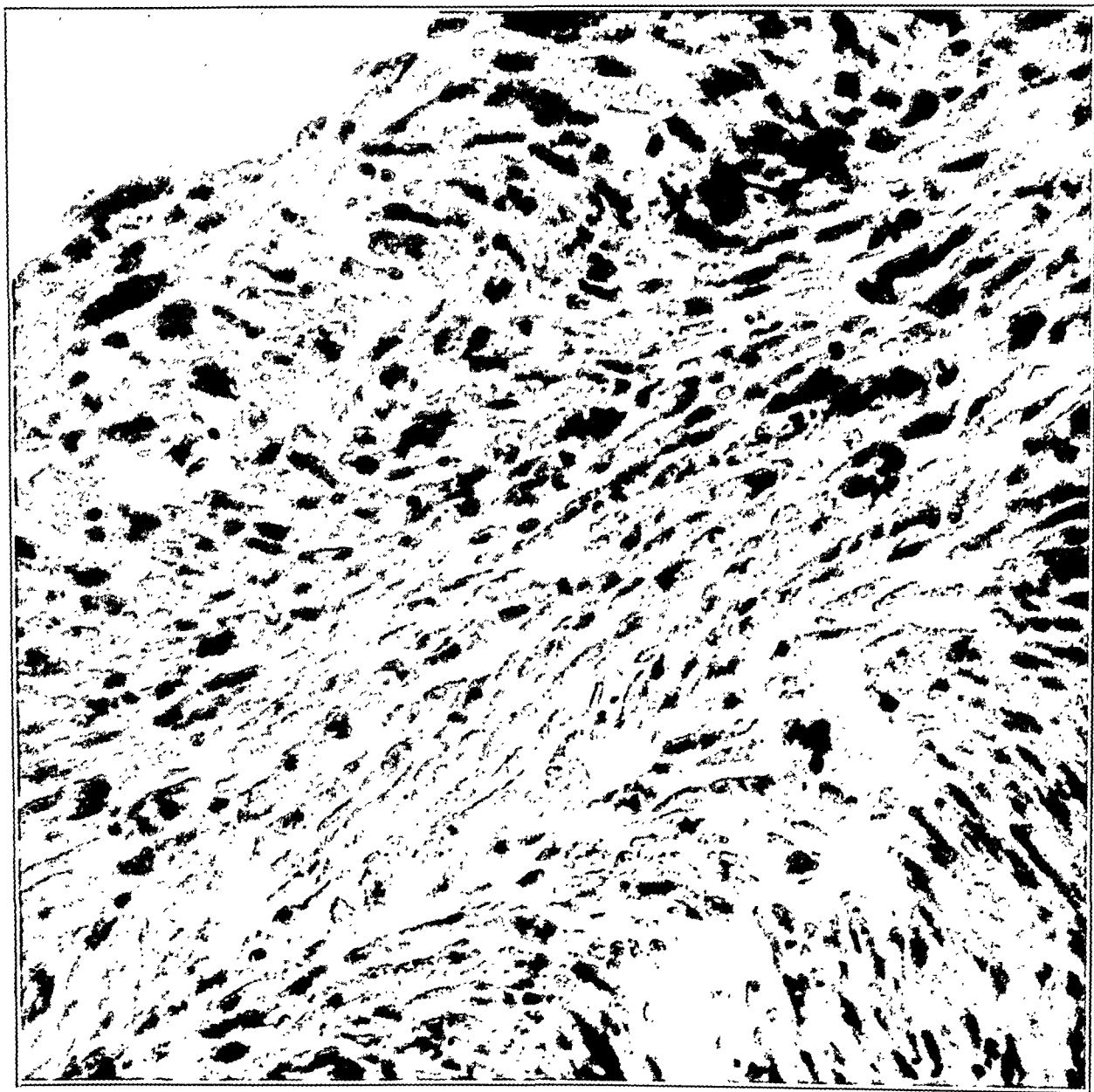


Fig. 38 (path. no. 26593).—Very malignant neurogenic sarcoma showing a microscopic picture predominated by crowded, elongated nuclei and tumor giant cells.

structure of the tumor is largely neurinomatous, radical amputation is indicated. In both of these groups of tumors just mentioned, the prognosis and indication for treatment differ markedly from primary sar-

coma of the bone in which the outlook for a cure is usually better than in tumors of the malignant neurogenic group, but worse than in neoplasms of the fibrosarcoma group.

OSSEOUS INVASION BY MISCELLANEOUS TUMORS OF CONNECTIVE
TISSUE ORIGIN

In addition to the fibrosarcomas and neurogenic sarcomas producing skeletal involvement, there may be in rare instances a similar clinical picture caused by some unusual form of tumor of the connective tissue series.

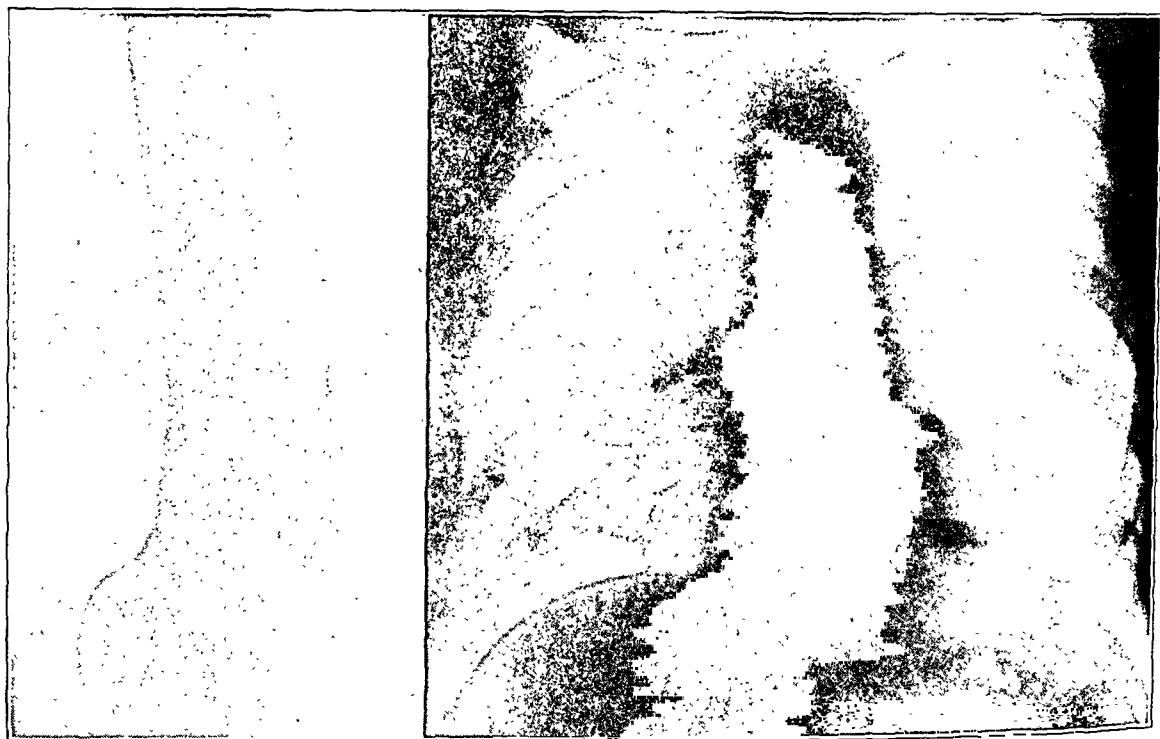


Fig. 39 (path. no. 25888).—A neurogenic sarcoma invading bone and producing pulmonary metastasis. Symptoms referable to the involved femur were present only five months, when the roentgenogram of the chest showed evidence of metastases. The patient died two months after the date of taking the films.

In a review of over seventeen hundred neoplasms involving the bone, after a complete study in which all cases with adequate data had been definitely classified, five such cases were found that could not be classed as either primary bone tumors or metastatic to the skeleton from other organs, and that were neither of the fibrosarcoma or neurogenic group. Three of these cases were classed as angiomatous, one as myosarcoma arising in the voluntary muscles and another as lipoma. These rare neoplasms of the bone are briefly reviewed here.

Angioma of the Bone.—While angioma of the bone is recognized by the Bone Registry of the American College of Surgeons as a definite entity, no verified angiomatous tumor is recorded in their collection. From the literature, particularly of the nineteenth century, it would appear that tumors of the hemangio-endothelial or hemangioma group are fairly common, but these older reports have in a large measure been discredited since they included many cases, either of carcinomatous metastases to bone, vascular forms of osteogenic sarcoma or neoplasms now recognized as belonging to the pathologic entity of Ewing's sarcoma or multiple myeloma (Howard and Crile³).



Fig. 40 (path. no. 25892).—A primary cavernous hemangioma of the upper end of the humerus, occurring in a white man, aged 25, following four years after trauma. The patient is living twelve years after a curettage and has full function of the arm (case of Dr. James Hitzrot). The roentgenogram illustrates the characteristic soap-bubble effect produced in the periosteal and cortical zones. There is no destruction in the marrow cavity.

Three benign hemangiomas of the bone (figs. 40-47) are recorded in the laboratory. One of these is of the cavernous type, occurring in a man, aged 25, in the upper end of the right humerus, with pain of two years' duration following trauma four years previously. The roentgenogram showed a peculiar soap-bubble effect extending into the periosteal zone and producing only slight erosion of the bone. At operation

3. Howard, W. T., and Crile, G. W.: A Contribution to the Knowledge of Endothelioma and Perithelioma of Bone, *Ann. Surg.* **42**:358, 1905.

a thin bone shell was found, and the tumor beneath had the appearance of an altered blood clot. The section showed a loose connective tissue stroma with dilated blood sinuses lined by endothelium and numerous peculiar connective tissue cells suggestive of sarcoma (see figs. 40-42). This case was reported by Dr. James M. Hitzrot⁴ of New York,

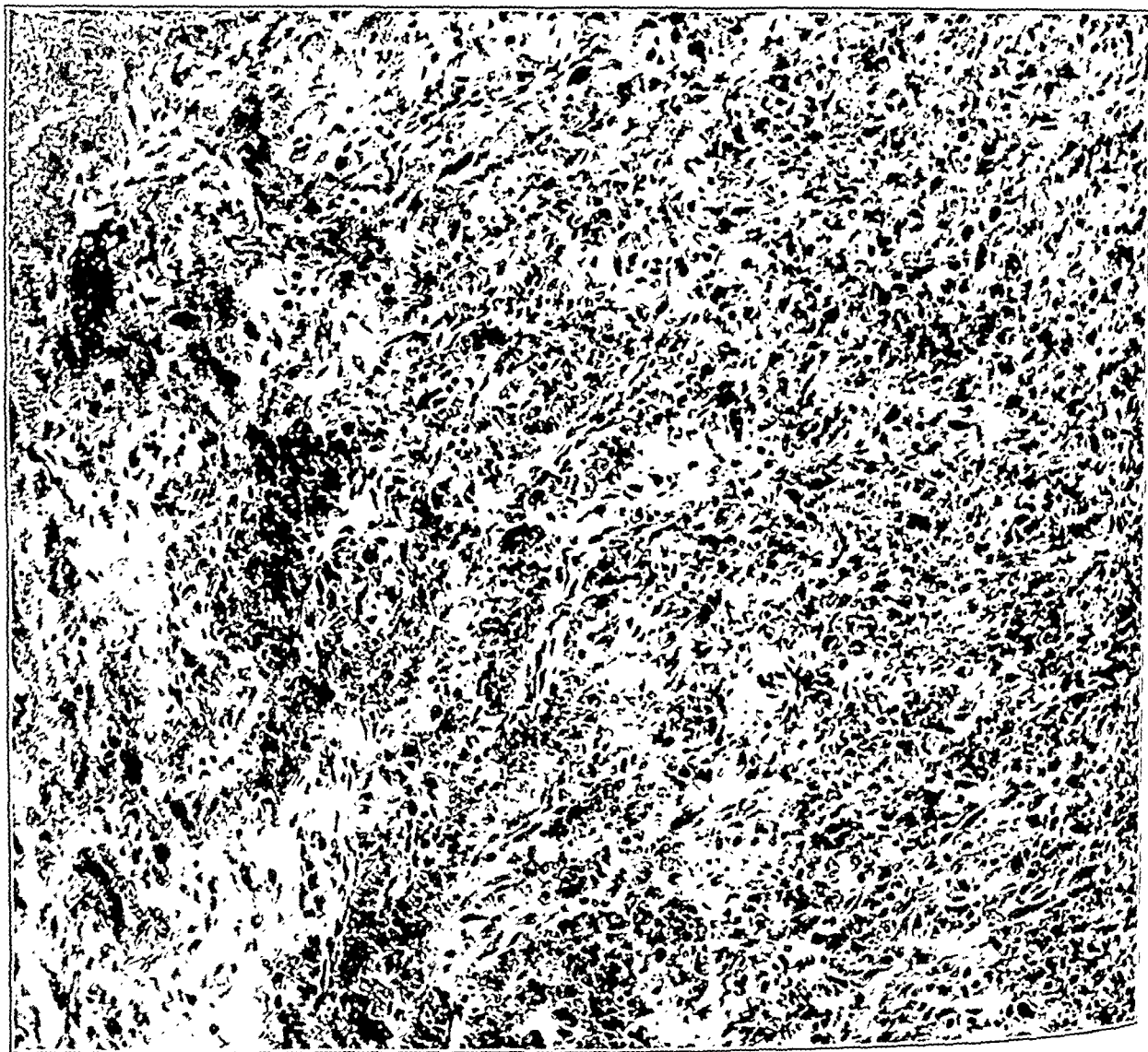


Fig. 41 (path. no. 25892).—Photomicrograph showing a cellular connective tissue area, with the development of a loose myxomatous substance and a lace-like branching of fibrous trabeculae (see fig. 40).

who appended a bibliography on vascular tumors reported in the older literature. Although only curettage was done in January, 1916, the

4. Hitzrot, J. M.: Haemangioma Cavernosum of Bone, *Ann. Surg.* 65:477. 1917.

patient (who is a surgeon) was reported as leading an active life with full use of the arm in 1928.

The second case of angioma was of the capillary type (figs. 43, 44 and 45) and occurred in the lower end of the ulna in a white youth, aged 20, following an injury to the right wrist eight months previously. The tumor grew rapidly and was of soft consistency. The neoplasm had the same loose soap-bubble effect in the roentgenogram. The lesion was



Fig. 42 (path. no. 25892).—Photomicrograph showing an area with dilated blood spaces lined by endothelium, about which connective tissue elements are proliferating (see fig. 40).

resected in September, 1926, and in the gross was composed of numerous irregular hemorrhagic cavities embedded in a white fibrous substance. The sections showed a mass of dilated capillaries lined by endothelium and surrounded by young connective tissue cells embedded in adult fibrous tissue. The patient was last reported well in September, 1929, three years after operation.

The third case (figs. 46, 47 and 48) occurred in the lower end of the humerus of a colored man, aged 52, who had had indefinite rheumatic complaints, supposedly for fourteen years, and pain with dysfunction for twelve months. There was a definite history of trauma, occurring three years before observation. Motion of the elbow was limited. The roentgenogram showed the same loose soap-bubble effect in the subcortical and subperiosteal regions. A local excision was performed in 1911, and



Fig. 43 (path. no. 38952).—A case of primary capillary hemangioma in the lower end of the ulna occurring in a white youth, aged 20, following eight months after trauma. The patient is living three years after a resection. The roentgenogram shows the characteristic soap-bubble, expansile lesion on the shaft side of the epiphyseal line. (Compare with figure 40.)

the tumor was removed in one piece. The tumor tissue was friable and in some places mushy, but was not described as hemorrhagic. Under the microscope the tissue resembled very markedly the cellular areas in the cavernous type of hemangioma previously described. There were many areas in which dilated capillaries were surrounded by a single layer of endothelial cells. The patient was discharged from the hospital in good

condition, but all attempts to trace him thereafter were futile, and nothing is known of the ultimate result.

These three tumors form a small but strikingly uniform group. All occurred in adults over 20 years of age; there was a history of trauma in each case, with a duration of symptoms varying from eight months to two years, and all involved bones of the upper extremities. The roent-

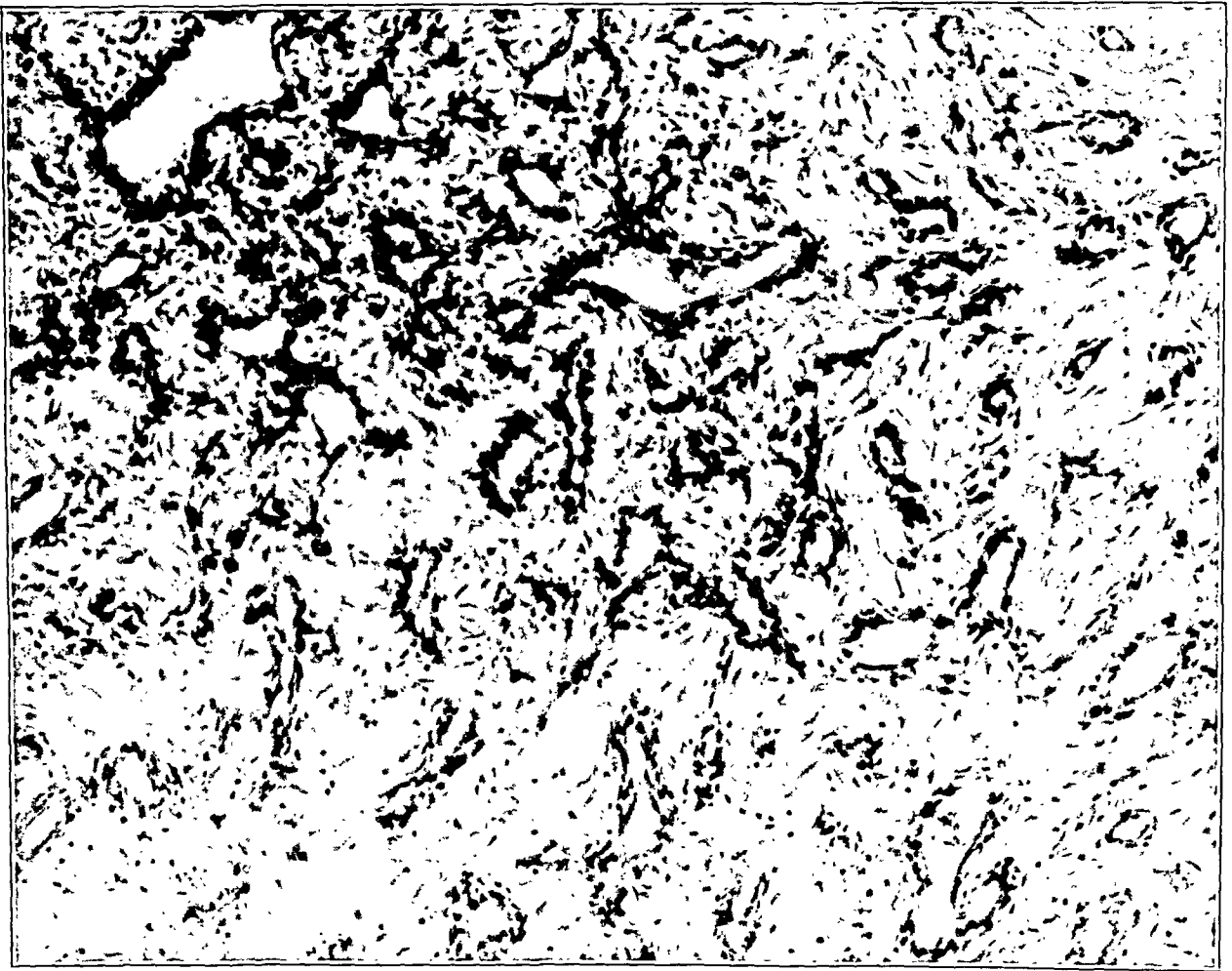


Fig. 44 (path. no. 38952).—Photomicrograph showing an area of dilated capillaries, lined by endothelium and surrounded by a loose connective tissue stroma (see fig. 43).

genogram in each case showed the same characteristic and unique soap-bubble effect. The coarsely multiloculated areas of rarefaction expand the shell of bone to paper-like thinness, but do not extend deeply into the medullary or cancellous spaces. The region of involvement is uniformly on the shaft side of the epiphyseal line and does not extend into the epiphysis. Microscopically, the three cases show histologic varia-

tions characteristic of the benign hemangiomas that are found in the soft parts or subcutaneous tissues. In no instance was death or metastases reported, although each of the patients had only a local operation. While included in this paper under tumors that involve bone by direct extension from the soft parts, it is not unlikely that the primary seat of the tumor was situated within the subperiosteal region of the bone in these cases.

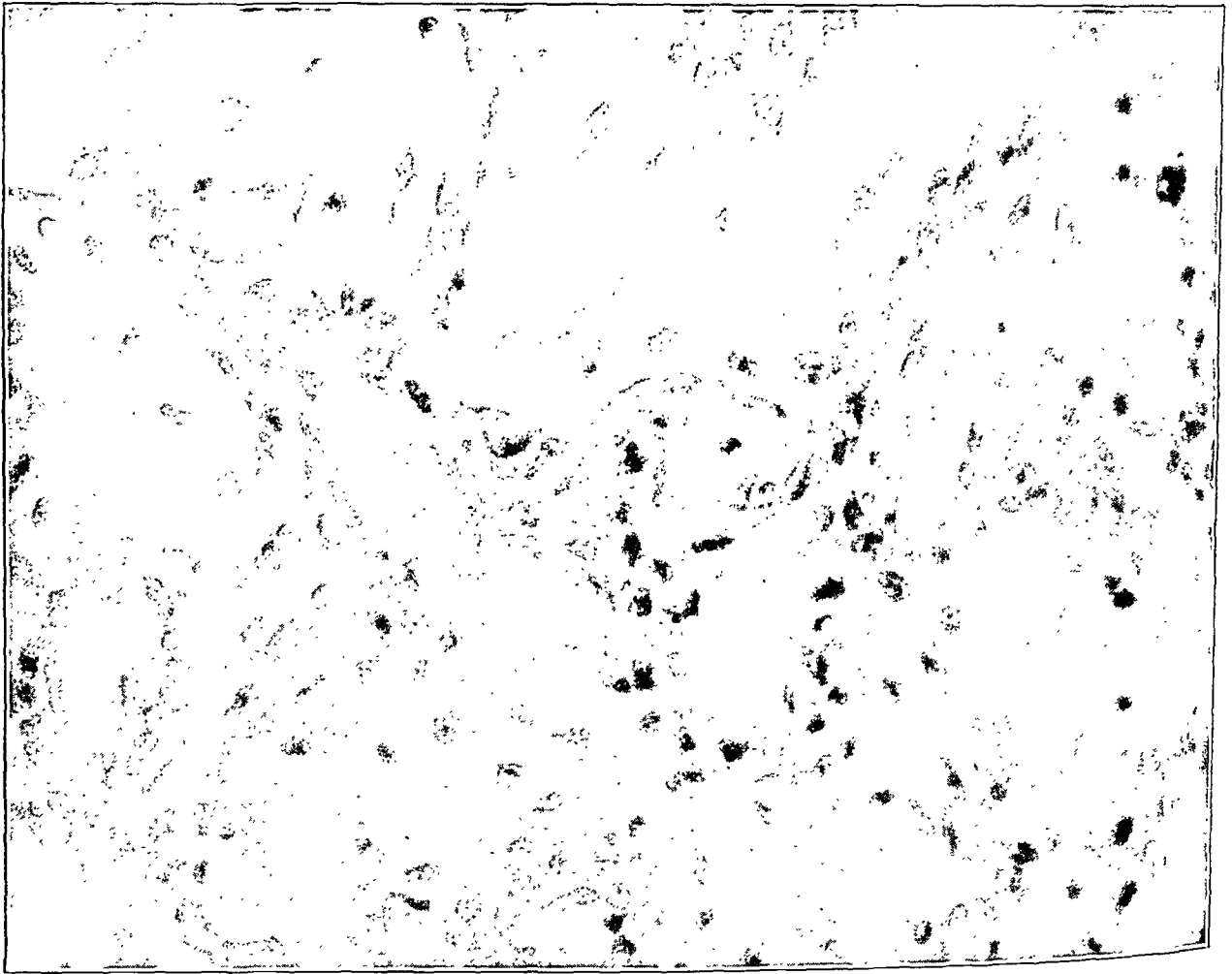


Fig. 45 (path. no. 38952).—High power photomicrograph of the area shown in figure 44. Note the tendency of capillary formation within the loose myxomatous syncytium.

It is important to note in studying the illustrations presented here that under the microscope these tumors were all predominantly of the connective tissue type containing numerous small spindle cells. They differ markedly from the usual hemangio-endothelioma (Kolodny⁵)

5. Kolodny, Anatole: A Case of Primary Multiple Endothelioma of Bone, *Arch. Surg.* 9:636 (Nov.) 1924.

reported in the literature in that they are single instead of multiple lesions, in that the regional lymph nodes are not involved, in that the tumors were not malignant and the cells are not of the epithelial-like type. The usual so-called hemangio-endothelioma reported are represented by four cases on file in this laboratory which were proved on careful study to be metastatic malignant pigmented moles without pigment, giving rise to multiple bone involvement and metastasizing to

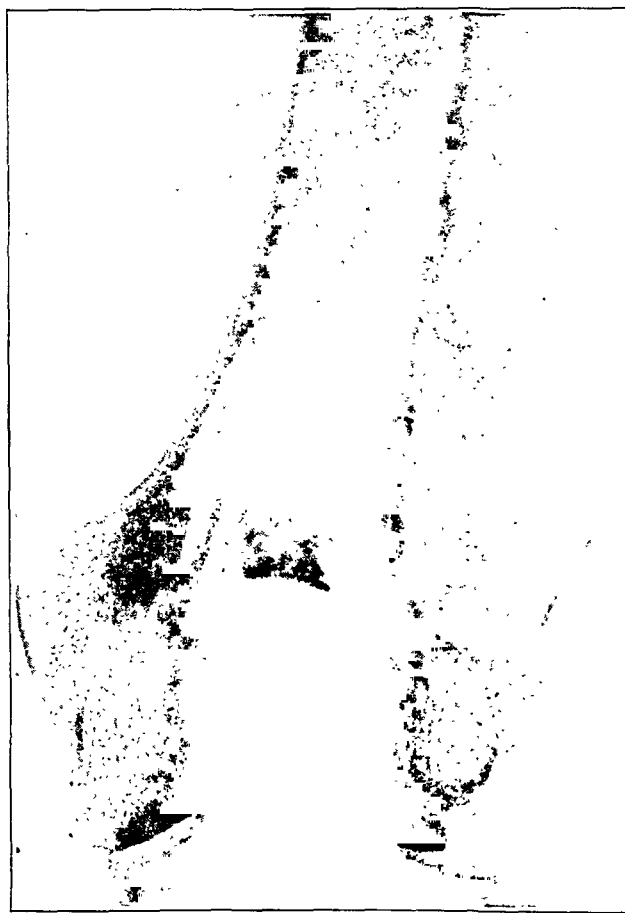


Fig. 46 (path. no. 35221).—A case of primary capillary hemangioma in the lower end of the femur, occurring in a colored man, aged 52, following three years after trauma. The patient was discharged well after a local excision performed in 1911 and has not been traced since. The foamy, coarsely multi-loculated appearance typical of benign angioma of bone is seen. (Compare with figures 40 and 43.)

regional lymph nodes. One of these cases is illustrated below (figs. 49 and 50).

Myosarcoma and Lipoma.—Two other cases are included here because of their rarity. One of these was a myosarcoma originating in the voluntary muscles in a white woman, aged 29, who had had recurrent

swelling following an injury to the lower end of the left femur four years previously. The swelling was removed by local operation in March, 1917, and the bone which was apparently slightly involved was scraped. A sinus persisted after the operation, and in the sinus a second tumor formed. This was excised in May, 1918, and had the appearance of an

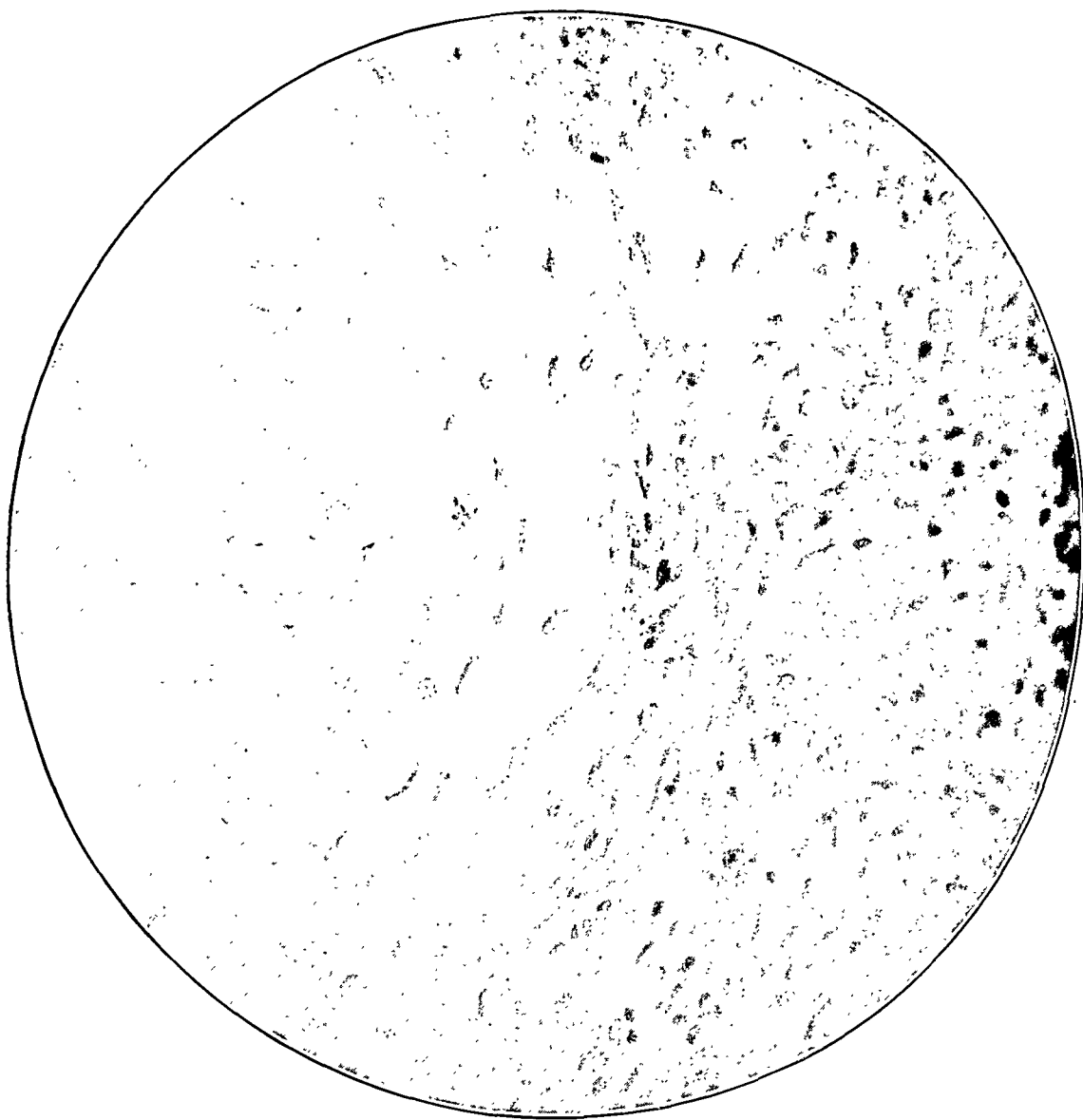


Fig. 47 (path. no. 35221).—Photomicrograph showing the loose connective tissue stroma and proliferation of connective tissue cells.

organized blood clot. A fungus-like growth again appeared in the wound, and in June, 1918, the leg was amputated. The gross specimen showed an apparently periosteal tumor extensively invading the underlying cancellous bone in the internal condyle of the femur.

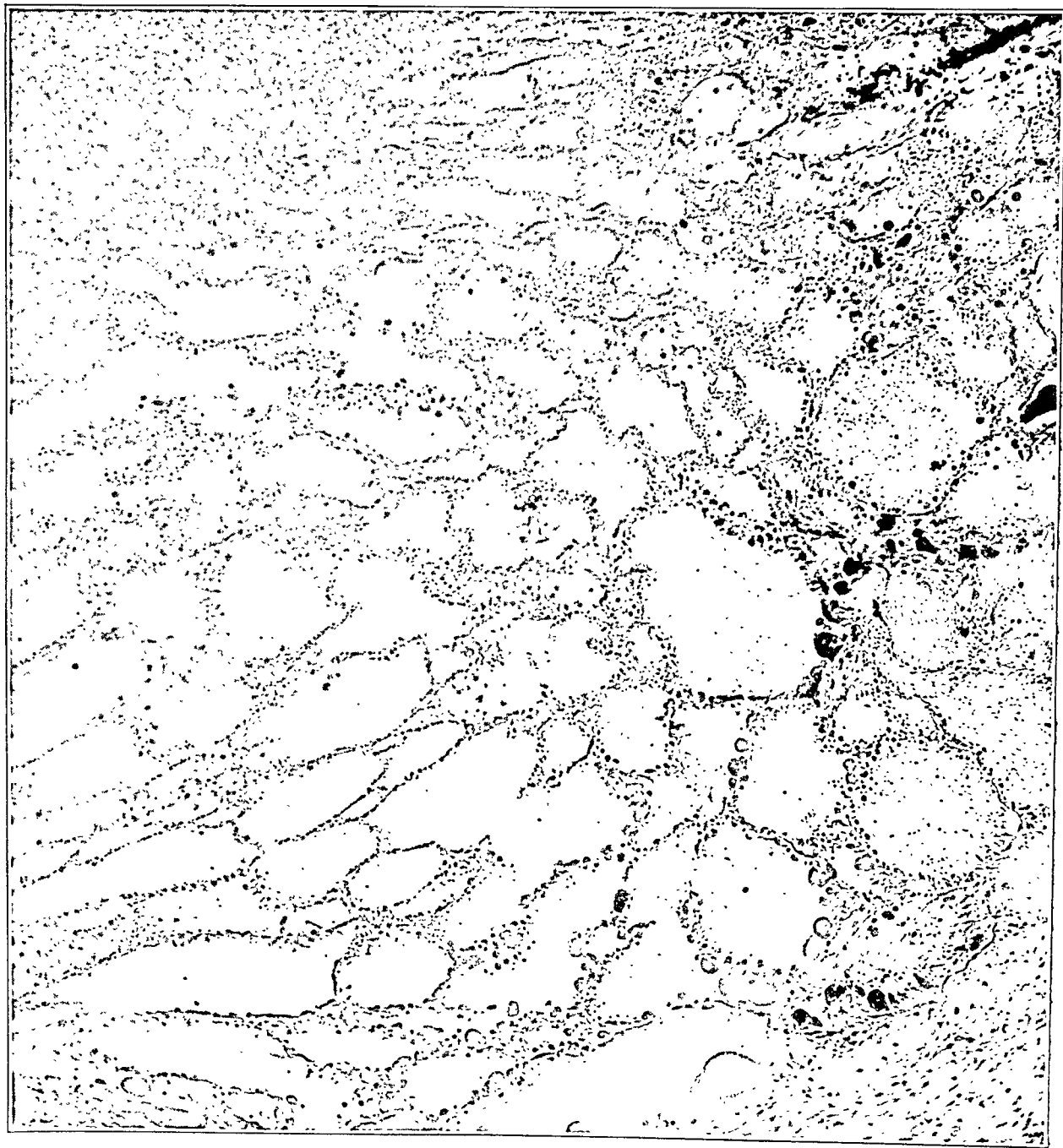


Fig. 48 (path. no. 35221).—An area of dilated capillaries.

The patient died three years and four months after the amputation with pulmonary metastases. Because of the relationship to bone and the fibroid reaction in the granulation tissue the tumor was originally classed as a fibrospindle sarcoma of the periosteum. However, under the microscope (fig. 51) a very distinct cellular picture composed of large cells with small nuclei enclosed in compartments formed by an eosin-staining reticulum was found. When cut in a longitudinal direc-



Fig. 49 (path. no. 48227).—A malignant pigmented mole metastasizing to bone and the regional lymph nodes.

tion, these cells had definite striations characteristic of voluntary muscle. The tumor was histologically identical with rhabdomyomas of other organs (heart, tongue, etc.) reported in the literature by Farber.⁶

The other case occurred in a white girl, aged 15, who had a swelling of one month's duration in the region of the knee joint. The roentgenogram showed a soft part swelling slightly eroding and roughening the

6. Farber, Sidney: Congenital Rhabdomyoma of the Heart, *Am. J. Path.* 7:105, 1931.

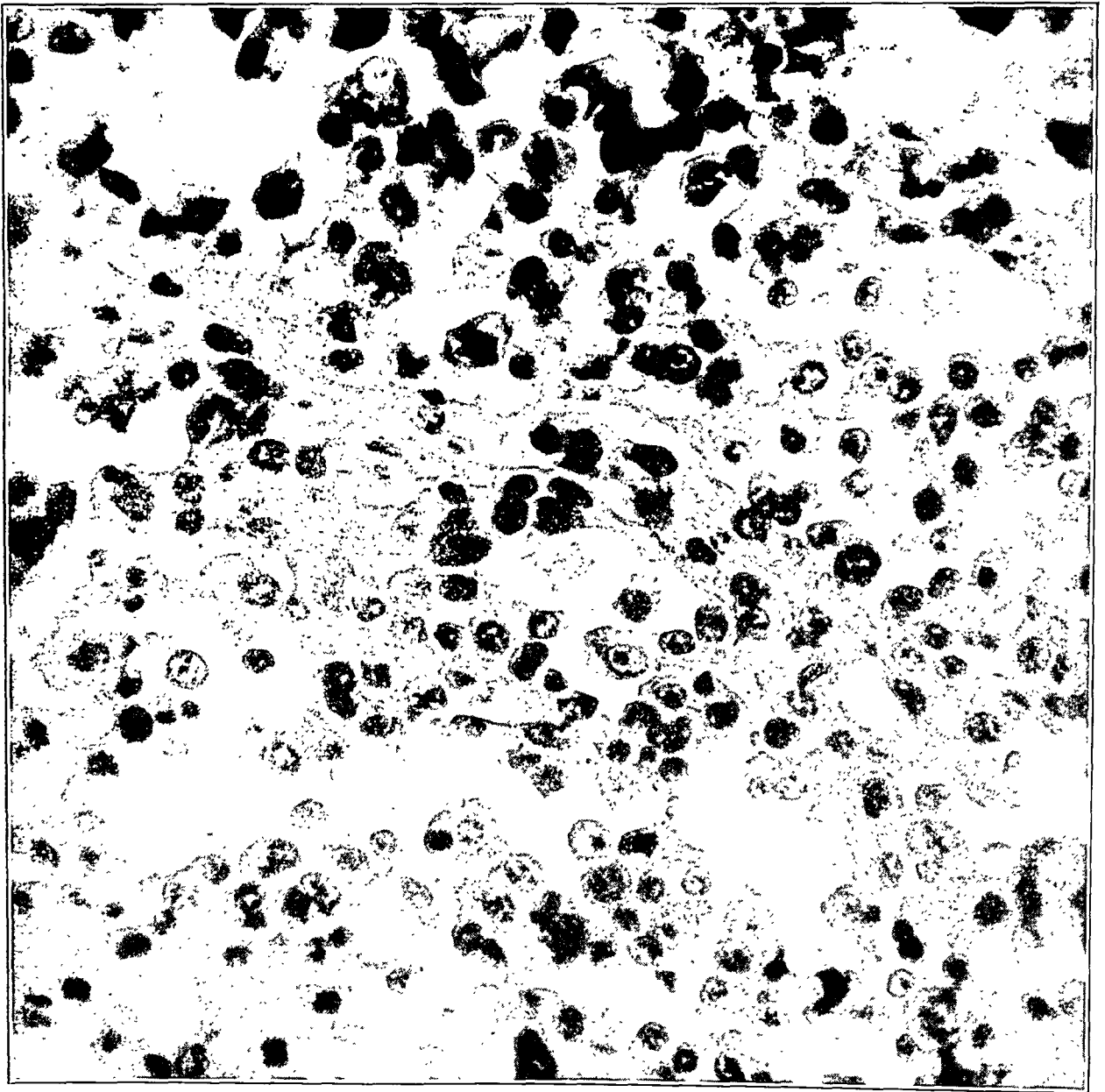


Fig. 50 (path. no. 48227).—Photomicrograph showing the cells of an epithelial-like character. No melanin pigment was seen in any of the sections, and the case was incorrectly diagnosed hemangio-endothelioma. Similar mistakes are reported in the literature under such a diagnosis.

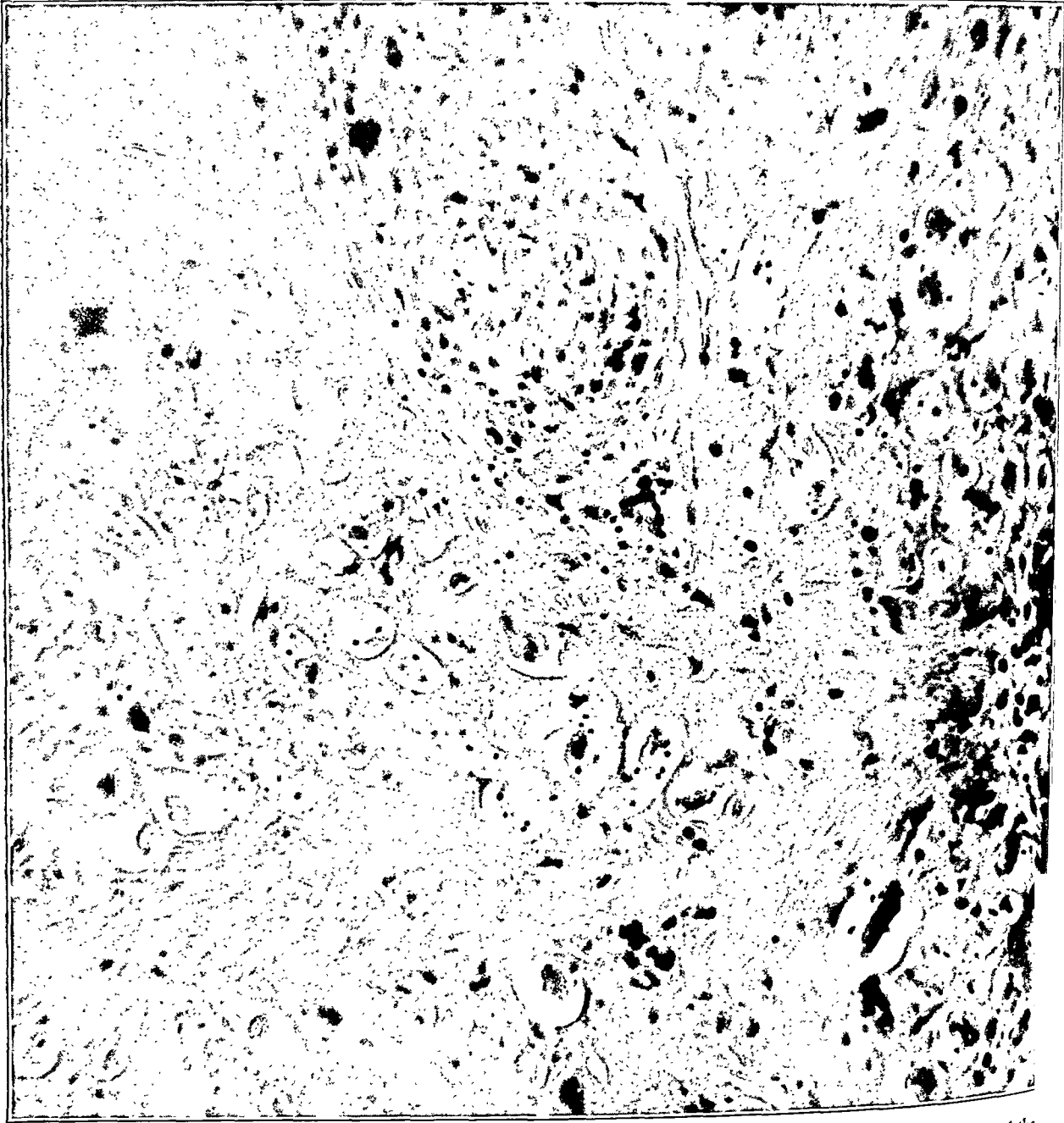


Fig. 51 (path. no. 23309).—Photomicrograph showing a sarcoma arising in the muscles around the lower end of the femur of a white woman, aged 29. The tumor invaded the bone, and the patient died of metastases three years after amputation. The photomicrograph shows the isolated muscle fibers with small nuclei cut at right angles and lying within small compartments (sarcolemma). Sections cut in the opposite direction show definite striations in the muscular fibers.

internal condyle of the femur. The sections showed a typical benign lipoma (figs. 52 and 53). A local operation was done, but the case is too recent to report the results of treatment. Two similar cases, which were distinctly benign, were recently reported by Edwin I. Bartlett,⁷ although Stewart⁸ reported instances of malignant bone involvement of supposedly liposarcomatous nature. The cases reported by Stewart, however, have a markedly different microscopic picture.

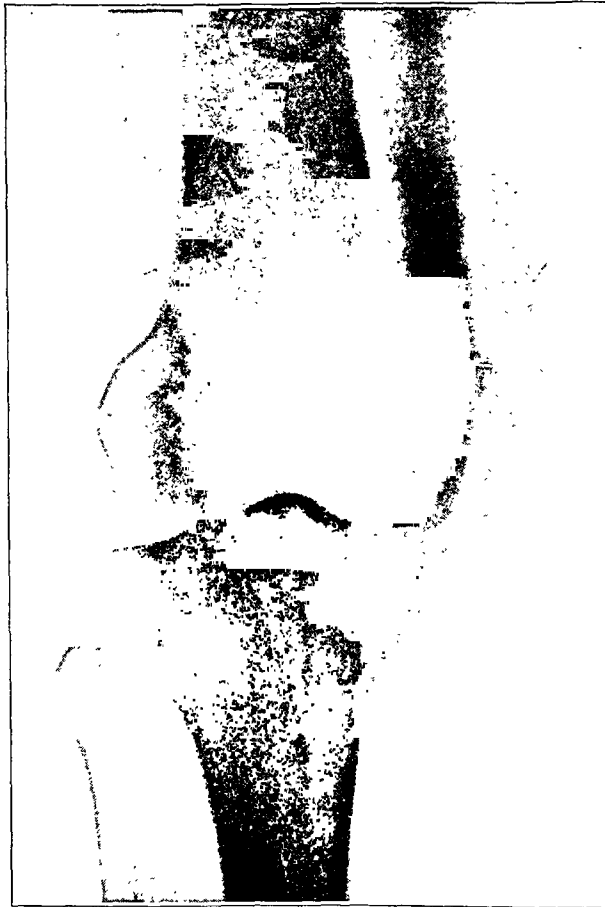


Fig. 52 (path. no. 44886).—A lipoma occurring in the knee joint and producing an erosion of the lower end of the femur. The soft part shadow and roughening of the external condyle of the femur are seen.

This small and miscellaneous group of connective tissue tumors involving the bone (nonosseous in origin and not metastatic in nature), although representing the odds and ends of a far larger collection of neoplasms primary in the bone, demonstrates the variety of conditions

7. Bartlett, Edwin I.: Periosteal Lipoma, *Arch. Surg.* **21**:1915 (Dec.) 1930.

8. Stewart, Fred W.: Primary Liposarcoma of Bone, *Am. J. Path.* **7**:87, 1931.

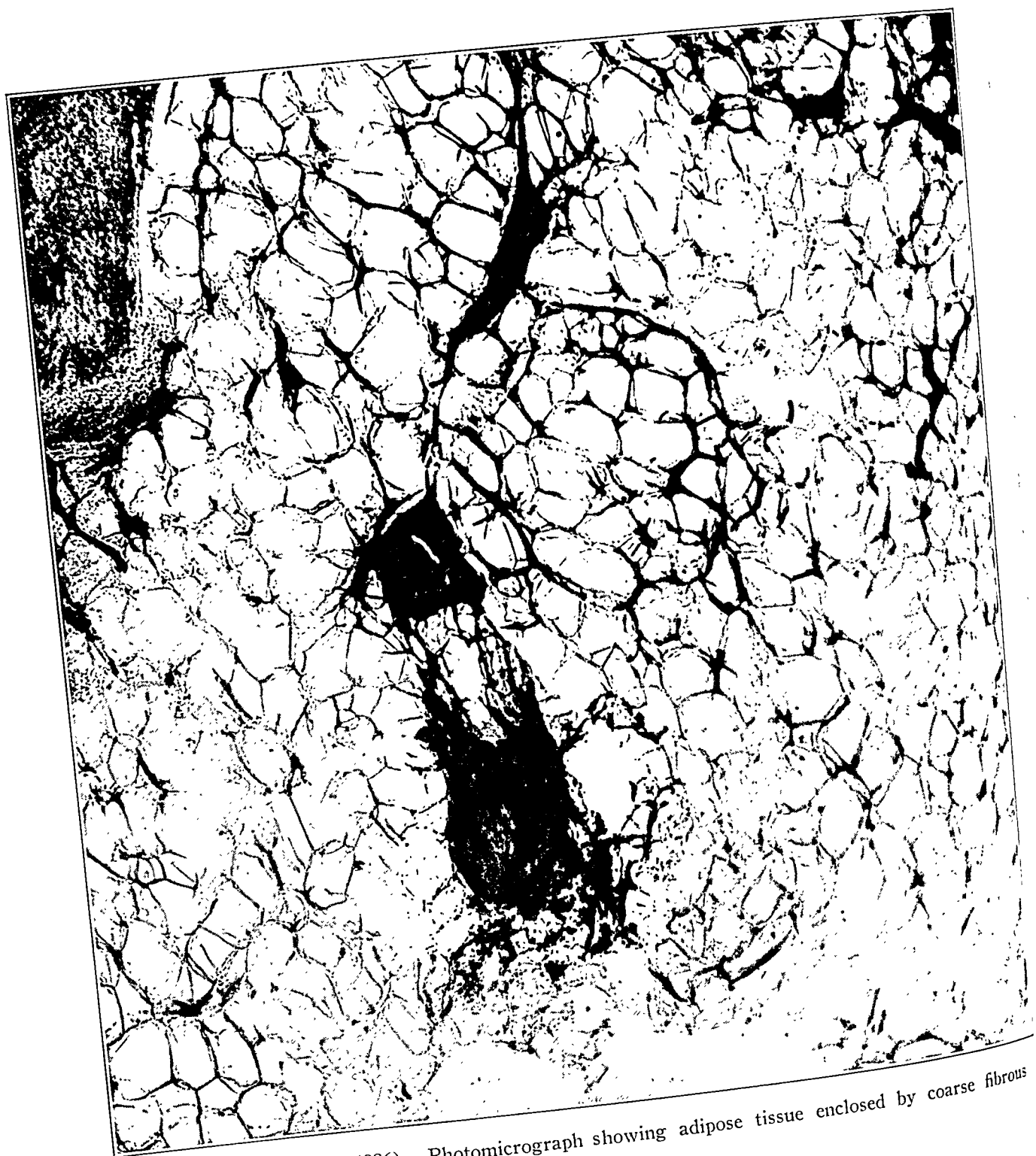


Fig. 53 (path. no. 44886).—Photomicrograph showing adipose tissue enclosed by coarse fibrous trabeculae.

under which neoplastic invasion of the skeleton may occur. When taken in conjunction with the fibrosarcoma and neurogenic sarcoma groups discussed in the early part of this paper, they indicate the importance of identifying pathologically the type of tumor producing the osseous involvement.

In all the cases reported in this paper, the initial diagnosis was usually incorrect, and even after the customary pathologic examination, the tumor was in most instances incorrectly classified. The prevalent tendency is to regard these neoplasms erroneously as primarily osteogenic, or to judge them too indiscriminately as fascial sarcoma. As a result, the prognosis and mode of treatment is often on an insecure and improper basis.

From the present study, however, it is clear that each of the various entities warrants individual treatment. In fibrosarcoma invading bone, not of the oat cell type, an attempt to eradicate the disease locally is justifiable, but amputation should be resorted to promptly after recurrence. In the oat cell type, primary amputation when possible is advocated. In the neurogenic sarcoma group producing osseous involvement, primary amputation is the treatment of choice. In angiomas of the bone, local excision is warranted, preferably reinforced by irradiation since this type of tumor when occurring in the soft parts or subcutaneously gives indication of radiosensitivity. For lipomas, local operation is indicated, and in rhabdomyoma, amputation.

A COMPLICATION OF TARRY LUTEAL CYSTS*

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The literature on blood cysts of the ovary presents a fascinating study, particularly the literature of recent years, and especially that relating to the tarry and the chocolate cysts. The greatest debate has been waged concerning the cysts that have an epithelial lining.

In 1899, Russell¹ described an ovarian cyst and said that it arose from an aberrant remnant of Müller's duct. In 1905, Pick² reported a case of adenoma endometrioides ovarii. Since then considerable interest has been taken in these structures. In 1917, Blair Bell³ suggested the term endometrioma, and Sampson has since used the term endometriosis.

In 1920, Sampson⁴ gave his classic description of the "perforating chocolate cysts" of the ovary. He suggested that they arose by the transplantation of pieces of uterine mucosa through the fallopian tubes on to the surface of the ovary, where they grew and developed.

During the last decade, an extraordinary interest in the condition has become manifest. The literature is colossal, and though many of the references are case reports only, several hypotheses have been advanced. It is unnecessary to discuss these in detail, since they have already been discussed by several writers.

The uterine origin of the cysts seems to have completely captured the imagination of most workers, and the hypothesis seems to be considered fact, although the evidence is circumstantial.

While attention has been focused on this aspect of the tarry cysts, another point of view has been considered by other investigators, who have showed that many of the tarry cysts are of luteal origin. As

* Submitted for publication, April 22, 1931.

1. Russell, W. W.: Aberrant Portions of the Müllerian Duct Found in the Ovary, *Bull. Johns Hopkins Hosp.* **10**:8, 1899.

2. Pick, L.: Ueber Neubildungen am Genitale bei Zwittern, nebst Beiträge zur Lehre von den Adenomen des Hodens und Eierstockes, *Arch. f. Gynäk.* **76**:191, 1905; Ueber Adenome der männlichen und weiblichen Keimdrüse bei Hermaphroditismus verus und spurius, *Berl. klin. Wchnschr.*, 1905, no. 17, p. 502.

3. Bell, W. Blair: *Principles of Gynaecology*, London, Baillière, Tindall & Cox, 1917.

4. Sampson, J. A.: Perforating Hemorrhagic (Chocolate) Cysts of the Ovary (Résumé), *Am. J. Obst. & Gynec.* **11**:526, 1921.

long ago as 1898,⁵ it was demonstrated that luteal cysts may develop a heterotopic lining of epithelium, and a similar lining was demonstrated in many of the tarry luteal cysts. The question that arises immediately is, Are these two varieties of tarry cysts different, or are they identical? In a recent paper, I⁶ attempted to show that the similarities between the cysts, the endometriomas (or endometriosis) and the tarry luteal cysts are remarkable. The inference is that they are identical. This is, however, not yet proved. The problem will be discussed further in another paper. The two cases of tarry luteal cyst reported here illustrate a complication that is thought generally to be characteristic of endometrioma. Similar examples were reported by Brakeman⁷ and Shaw,⁸ and a related condition was referred to by Johnson,⁹ but since so much emphasis has been laid on the endometriomas and their complications, no opportunity of assisting in a restoration of balance of opinion should be lost.

REPORT OF CASES

CASE 1.—B. E., unmarried, aged 27, complained that she had not been feeling well for the seven months before examination. At first she had merely felt tired in the evening. Two months before being examined, she had an attack of "influenza" associated with pains all over the body and persistent vomiting for five days. Her tongue was coated, and the abdomen was swollen, but there was no localized abdominal tenderness. She was constipated, and the feces were offensive. She recovered, but on having a similar attack, came to the hospital for treatment. Her menstrual history was normal.

On examination, she was somewhat pale. There was a slight, generalized soft swelling of the abdomen with tenderness in both iliac fossae. Pelvic examination disclosed a small mass in the right fornix and a thickening of the left fornix and pouch of Douglas.

On operation, a large number of adhesions of the omentum were found to the back of the uterus. There were also a number of cysts, varying in size from minute structures to one or two which were from 1 to 1½ inches (2.5 to 3.8 cm.) in diameter. The cysts contained a yellowish fluid, and two or three contained old blood. A number of small tarry cysts were found in the right ovary. There were dense adhesions in the pouch of Douglas. The ovary, tube and omentum were removed.

Pathologic examination of the right ovary, which was twice as large as normal, disclosed a number of cysts; some contained blood, and on the walls of two was a marked yellow layer. Microscopically, the walls showed luteum-like cells in various stages of retrogression. None of the cysts showed a heterotopic epithelial

5. Fraenkel, L.: Der Bau der Corpus-luteum Cysten, Arch. f. Gynäk. **56**:355, 1898.

6. King, E. S. J.: The Morphological Similarity of Certain Luteal Cysts and Endometriosis of the Ovary, Surg., Gynec. & Obst. **45**:1, 1930.

7. Brakeman, O.: Beitrag zur Klinik und Pathologie der Teercysten des Eierstockes, Arch. f. Gynäk. **129**:632, 1927.

8. Shaw, W.: Some Pathological Forms of the Corpus Luteum, J. Obst. & Gynec. Brit. Emp. **34**:300, 1927.

9. Johnson, W. C.: Peritoneal Reaction to Contents of Ruptured Hemorrhagic Cyst of the Ovary, Proc. New York Path. Soc. **23**:142, 1923.

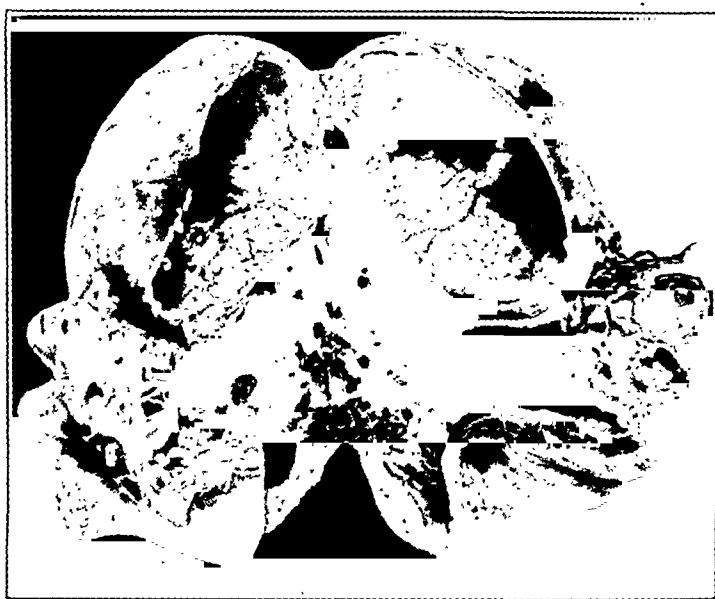


Fig. 1 (case 2).—The bilocular tarry luteal cyst removed from the site of the right ovary.



Fig. 2 (case 2).—Photomicrograph of a portion of the wall of a cyst which was removed from the site of the left ovary. Luteal cells are present; $\times 110$.



Fig. 3.—Photomicrograph of another portion of the wall showing an epithelial-lined "gland" communicating with the cavity of the cyst; $\times 110$.



Fig. 4.—Photomicrograph from the secondary nodule in the wall of the sigmoid colon; epithelial-lined spaces and a blood cyst are present; $\times 35$.

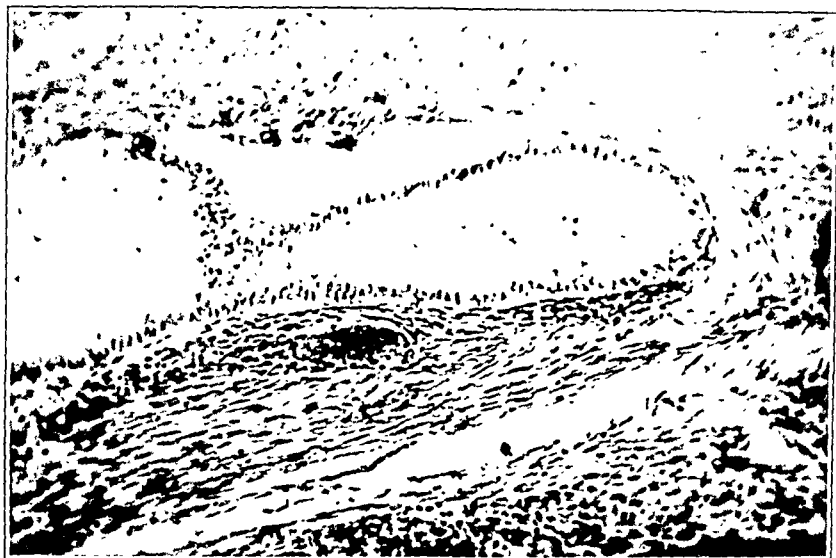


Fig. 5.—Higher power view of portion of one of the “glands” shown in figure 4; $\times 110$.

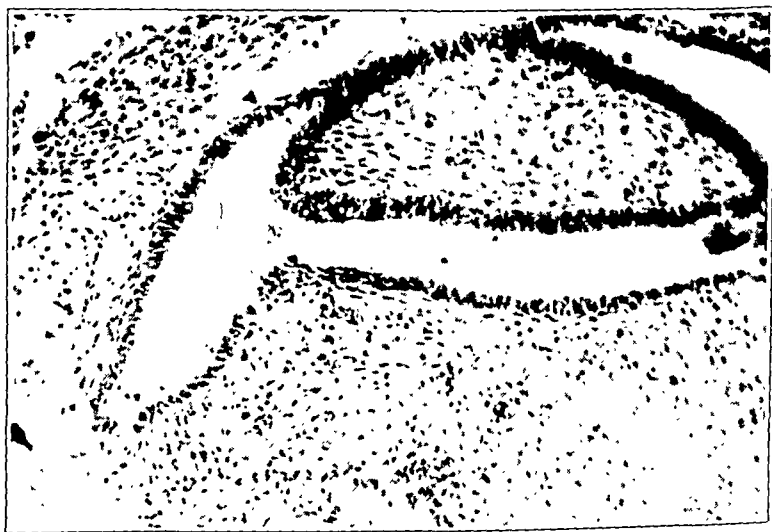


Fig. 6.—Another portion of the same nodule showing the nature of the epithelium; $\times 110$.

lining. The cysts in the omentum were thin-walled and showed cells in the walls similar to those in the luteal cysts of the ovary, but in this case they were probably phagocytic. In one or two of the cysts there was a lining of columnar cells. The dense tissue in the rectovaginal septum also showed some of these cells.

CASE 2.—J. M., aged 17, was admitted to the hospital with a complaint of pain in the hypogastric region of four days' duration occurring every fortnight. This pain commenced when she was 14 years of age. There had been an absence of menstrual flow. The patient had been partially blind and deaf in one ear for years.

On examination, it was found that the sight was definitely impaired owing to interstitial keratitis. Punched-out ulcers were present on both legs. The chest was normal. There was a large oval midline tumor rising out of the pelvis and extending to just above the umbilicus.

On pelvic examination, the cervix could not be felt. The uterus was in the normal position, not enlarged and adherent to the anterior tissues.



Fig. 7.—Photomicrograph taken from the same section showing an epithelial-lined space and a small "gland" space. Calcification is present; $\times 75$.

Under an anesthetic, vaginal examination with a speculum showed a normal mucous membrane but no cervix uteri in the vault. There appeared to be a fold of mucous membrane in the region of the uterus. A sound was passed in this region, and about 2 ounces (59 cc.) of brownish fluid escaped.

Later, an exploration of the abdomen was performed. The large swelling found clinically proved to be a bilocular blood cyst of the right ovary. This was removed, together with the fallopian tubes.

The cyst of the ovary was ovoid, measuring 10 by 9 cm. in diameter. On section, it was found to contain chocolate-colored material and to be bilocular (fig. 1). The walls were 5 mm. in thickness.

Microscopic section of the wall showed that the cysts were luteal. Luteal cells of a somewhat atypical character were present in most portions of the wall. There was no epithelial lining. The fallopian tubes showed some aplasia of the epithelium.

Six months later, the patient returned to the hospital, having had pain during the intervening period. There had been no vaginal discharge at any time.

Examination disclosed tenderness in both iliac fossae, and in the midline in the suprapubic region. On pelvic examination, a mass could be felt in the pouch of Douglas, extending toward the left side. This was diagnosed as a cyst of the left ovary.

On operation, the uterus was found to be of about normal size. The right ovary was slightly enlarged and the site of a blood cyst. There was a small blood cyst on the wall of the sigmoid colon.

The uterus, right ovary and nodule on the sigmoid colon were removed.

The uterus was slightly larger than normal and globular. It contained a small amount of tarry material. The site of the previous attachment of the fallopian tubes was intact.

Microscopically, the endothelium showed considerable aplasia.

The ovary was enlarged, measuring 2 by 2 by 1½ inches (5 by 5 by 3.8 cm.) in diameter. It contained a number of blood cysts. Microscopically, these were luteal cysts in various stages of retrogression; in their walls were epithelial "glands," and in some places the inner surface was lined by tall columnar epithelium.

A nodule from the sigmoid colon was irregularly spherical and measured 1.5 cm. in diameter. On section, it was found to contain a number of cystic spaces filled with blood. Microscopically, it consisted of a number of small blood cysts lined with tall columnar epithelium, and in the wall beneath the epithelium there was a "stroma" of small round cells and spindle cells. In many places there were "glands." Hematogenous pigmentation was present in the tissue in some places.

COMMENT

The discovery of peritoneal cysts secondary to tarry or chocolate cysts of the ovary usually leads to a diagnosis of endometriosis.

The observation made by several workers that tarry cysts of luteal origin may also produce such secondary cysts renders a thorough examination of any blood cyst of the ovary essential before a definite diagnosis may be made. It also raises the question whether an unquestioning acceptance of the uterine origin of the "endometrial" cyst of the ovary is not a perilous attitude.

In both of the cases reported in this paper, the nature of the ovarian cysts was demonstrated conclusively by the discovery of luteal tissue in their walls. Not all cysts of the luteal type are easy to diagnose, e. g., the corpus albicans cysts, in which the luteal cells have been replaced by hyaline tissue. In cases 1 and 2, however, this difficulty does not arise.

Another important point was the relationship of the columnar epithelium present in case 2 to the cavity of the luteal cyst. Luteal bodies are of common occurrence in the ovary, and the presence of both the luteal tissue and the endometrium-like epithelium could conceivably have been accidental or incidental. Serial sections, however, showed that the columnar epithelium lined, in part, the wall of the luteal cyst.

In a number of places crypts were present in the wall, and the epithelium lining these was cut across, giving the appearance of "glands." Fortunately, a number of these were cut longitudinally so that their continuity with the epithelium lining the wall of the cyst was indisputable. In some sections, however, there was no evidence that the "glands" were related to the epithelium in the luteal cyst, and in the absence of the evidence obtained from serial sections they would have been labeled "endometrial."

In tarry luteal cysts of the ovary only a marked reaction of the peritoneum to the spilt material may occur, as has been described by some writers,¹⁰ but in other cases epithelial-lined cysts may develop.

The effect on the peritoneum of the spilling of the contents of the cysts, with the development of secondary epithelial-lined cysts in the cases described, is particularly worthy of note, since the dense fibrous tissue reaction associated with the rupture of "endometriomatous" cysts has frequently been observed, but the fibrosis associated with tarry luteal cysts has been recognized only occasionally.

One important feature in case 2, from the point of view of Sampson's hypothesis, was the condition of the uterus. There was atresia of the os uteri, and therefore obstruction to the outflow of menstrual blood. This was an ideal case for retrogressive flow through the fallopian tubes or veins. There was, however, no evidence that blood was flowing through the tubes. These were removed after the first operation, and yet cysts developed in the other ovary and on the sigmoid colon.

More direct evidence was present in the aplastic condition of the endometrium and also in the luteal nature of portions, at least, of the walls of the cysts.

10. Brakeman (footnote 7). Johnson (footnote 9). Shaw (footnote 8).

RETROPERITONEAL LIPOMA

REPORT OF A CASE IN WHICH THE TUMOR WEIGHED
TWENTY-TWO AND ONE-HALF POUNDS *

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AND

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Several years ago Greensfelder and one of us (Dr. Bettman) reported a case of retroperitoneal lipoma¹ and reviewed the literature to that date. We found that von Wahlfendorf² had collected 166 cases of retroperitoneal lipoma, and that at about the same time Lecéne³ had reported 113 cases of solid paranephric tumors of which many were lipomas. Besides the cases of these two authors we were able to collect 16 other cases: Masson and Horgan,⁴ 12 cases; Holmes,⁵ 1 case; Hirsch and Wells,⁶ 1 case of their own and 1 case of McConnell's,⁷ and Heppner,⁸ 1 case. Most of these cases had been published after von Wahlfendorf's article went to press. At this time we wish to present another case of our own and to review briefly 11 cases that have appeared in the literature since the publication of our last article.

REPORT OF CASE

History.—A man, aged 40, entered the hospital on April 17, 1930, because of an abdominal enlargement of from six to seven months' duration, associated with weakness and heart burn. For fifteen years he had had "stomach and bowel

* Submitted for publication, May 19, 1931.

* From the Surgical Service of the Michael Reese Hospital.

1. Greensfelder, L. A., and Bettman, R. B.: Retroperitoneal Lipoma, Surg., Gynec. & Obst. **37**:468 (Oct.) 1923.

2. von Wahlfendorf, A. L.: Ueber retroperitoneale Lipome, Arch. f. klin. Chir. **115**:751 (May) 1921.

3. Lecéne, P.: Les tumeurs solides para-néphritique, Rapport assoc. franç. de chir., XXVIII Congress, Paris, Oct. 10, 1919.

4. Masson, J. C., and Horgan, E. J.: Retroperitoneal Lipomata, S. Clin. North America **1**:1451, 1921.

5. Holmes, Walter R.: Retroperitoneal Perirenal Lipomas, J. A. M. A. **75**: 1065 (Oct. 16) 1920.

6. Hirsch, E. F., and Wells, H. G.: Retroperitoneal Liposarcoma, Am. J. M. Sc. **159**:356 (March) 1920.

7. McConnell: Recurrent Liposarcoma of Kidney, J. M. Research **19**:225, 1908.

8. Heppner, E.: Large Retroperitoneal Lipoma with Sarcomatous Degeneration, Ztschr. f. Urol. **14**:14, 1920.

trouble" which consisted of attacks of abdominal cramps and frequent (from six to seven times daily) watery stools. He had noticed a gradual enlargement of his abdomen during the last half year. He had had "dizzy spells" and lately had been slowly getting weaker. He was able to continue work, however, until almost the date of admission to the hospital. He volunteered the surprising fact that although his abdomen was so definitely increasing in size he was gradually losing weight, 20 pounds (9 Kg.) in the last five years. On careful questioning, he admitted vague symptoms best described as abdominal discomfort.



Fig. 1.—Photograph of the tumor and attached kidney immediately after operation (posterior surface). Note the relative size of the mass as compared to the attached kidney and 8 inch retractors.

Examination.—Examination revealed a thin white man weighing 156 pounds (70.8 Kg.), with a protruding abdomen in startling comparison to his general emaciation. His complexion was pasty. His cervical, axillary, epitrochlear and inguinal lymph glands were palpable but small, firm and distinct. Examination of the chest revealed no abnormality other than that the base of the right lung was about 2 inches (5 cm.) higher than the left. The heart was slightly enlarged. The extremities were normal. There were no varicose veins, and the ankles did not swell on standing.

The abdomen was well rounded and on first sight suggested the distention occasionally seen in a case of marked paralytic ileus. On palpation, however, it was readily ascertained that the distention was due to the presence of a hard, firm, smooth mass apparently directly under the muscles. The mass projected from under the entire right costal margin and extended to the midline from the xyphoid to the umbilicus. The upper and lower left portions of the abdomen, as well as a very small area in the lower right quadrant, were softer on palpation and tympanitic on percussion and apparently contained intestines. In the midline of the abdomen there seemed to be a definite groove in the mass. The mass in the left side felt exactly the same as it did on the right and apparently was part of the same tumor. No mass could be palpated in the left lumbar region. Rectal examination was negative except for a slight prostatic hypertrophy. There were no abdominal varices and no scrotal varicocele.

Roentgen examination showed that practically the entire gastro-intestinal tract was crowded over to the left side of the abdomen, while the entire right side and a portion of the left were filled with a mass which cast a dense homogeneous shadow. An intravenous pyelogram showed the right kidney and ureter to be displaced downward and inward. Catheterized specimens of urine from both ureters were normal. The temperature, respiration and pulse rate were normal. The blood count was normal as to both numbers and types of cells.

Diagnosis.—The vagueness of the symptomatology, the length of duration of the abdominal tumor with the apparent slight discomfort and but recent loss of strength and particularly the roentgen picture immediately recalled to our minds the case previously reported. We felt that a tumor of the kidney could be ruled out by the form and position of the tumor, and by the groove at about the midline where it extended over to the left side of the abdomen. This groove we thought could best be explained by pressure of the mesenteric vessels in a retroperitoneal tumor. We thought that a mesenteric cyst could be ruled out because of its apparent origin in the right flank, its firm consistency and its immobility. A primary malignant condition could be discounted because of the great discrepancy between the size of the tumor and the lack of symptoms. The most likely benign, retroperitoneal tumor of such size, arising apparently from the right perirenal region, of the shape and consistency of this tumor, apparently crossing the midline of the abdomen behind the mesenteric vessels and giving as few symptoms as this tumor, would be a retroperitoneal lipoma. We therefore made the diagnosis of a retroperitoneal lipoma and advised operation.

Operation and Course.—Operation was performed under spinal anesthesia, 250 mg. of procaine hydrochloride being used. A transverse incision was made starting in the midline a few centimeters above the umbilicus and extending laterally and slightly upward into the right flank, cutting successively through skin, subcutaneous tissues, fascia and muscles. The peritoneum was carefully opened, and a large, firm, fatty tumor presented. It was immediately recognized that a larger opening was needed, and so the incision was extended to the left side in a similar manner as to the right. Even then the opening was not sufficient until a perpendicular incision was made in the midline extending upward for 2 or 3 inches (5 or 7.6 cm.). It could now be seen that this large tumor, apparently a typical lipoma, occupied the greater part of the intra-abdominal cavity. It was not adherent anteriorly. It was covered with a venous network, some of the veins being the size of the little finger. What seemed to be the anterior portion of the capsule was in fact the posterior peritoneum. The intestines were crowded over to the left, as shown by palpation and the x-rays, and the root of the mesentery had caused a definite groove at the midline.

The posterior peritoneum was incised near and parallel to the crowded over, ascending colon as in mobilizing the ascending colon in the operation of colectomy. The tumor was then freed as much as possible by blunt dissection. Great care was taken at the portion of the tumor in which the mesenteric vessels lay, lest they be cut, an accident which accounts for a large percentage of the primary mortality recorded in the literature. After this had been done the dissection was carried over into the flank. The ureter was found lying in a deep groove in the tumor. The kidney was almost completely surrounded by the mass, while the renal artery and vein seemed entirely buried. It was felt that the technical difficulties of freeing the vessels were so great that the risk involved was not justifiable in view of the perfect function of the opposite kidney, so that the renal artery and vein were



Fig. 2.—Anterior surface. Note the many large collapsed veins.

firmly ligated and cut close to their junction with the aorta and vena cava, and the kidney was removed with the tumor. The ureter was ligated close to the bladder and cut. The main blood vessels to the tumor seemed to arise from the perirenal region. These were clamped and cut, and the tumor was removed. A stab wound for drainage purposes was made in the right flank. The cut edge of the posterior peritoneum, close to the ascending colon, was sutured into the flank, closing the raw surface left after the removal of the tumor and bringing the colon back approximately to its normal position.

A transfusion of 250 cc. of whole blood was given before and after the operation. The patient left the operating table in none too good a condition, but promptly rallied and made a speedy and uneventful recovery.

Pathologic Changes.—The pathologic report made by Dr. Otto Saphir was as follows: "The specimen consists of tumor with attached kidney and ureter, measuring 50x25x25 cm. in its greatest diameters and weighing 22½ lbs. The tumor in most portions has the appearance of fat. In some portions it is fairly firm in consistency; in others it is soft and gelatinous. In these latter portions the tumor appears to be degenerating. One portion of the tumor shows the fatty appearance to be somewhat obscured by a dull brown color. The consistency here is fairly firm. The entire tumor is covered by a thin membrane. The kidney is apparently normal."

Microscopic Observations.—The microscopic report was as follows: "Some of the sections reveal a marked new formation of fat tissue, with many small indistinctly outlined signet-shaped cells. Other sections show throughout the fat tissue a moderate number of spindle-shaped cells and connective tissue fibers extending in various directions. Other fields show the presence of a pink-stained mucinous



Fig. 3.—The patient two weeks after operation. The incision is marked with mercurochrome-220 soluble so as to photograph more clearly. Ten months after operation the patient was found working at his trade as an iceman and carrying heavy blocks of ice up three and four flights of stairs without discomfort and with no signs of hernia.

material with many stellate-shaped cells. Other portions again reveal many lymphocytes and endothelial cells which are found infiltrating the connective tissue fibers and fat tissue. Sections reveal that the fat tissue constitutes the largest portion of the tumor."

In our former article we briefly reviewed the literature up to that date. Since then we have found the following cases:

Stratton⁹ reported a case of retroperitoneal lipoma in a woman aged 39. The tumor was situated in the left side of the pelvis. It

9. Stratton, F. A.: Retroperitoneal Tumors, Wisconsin M. J. 22:260 (Nov.) 1923.

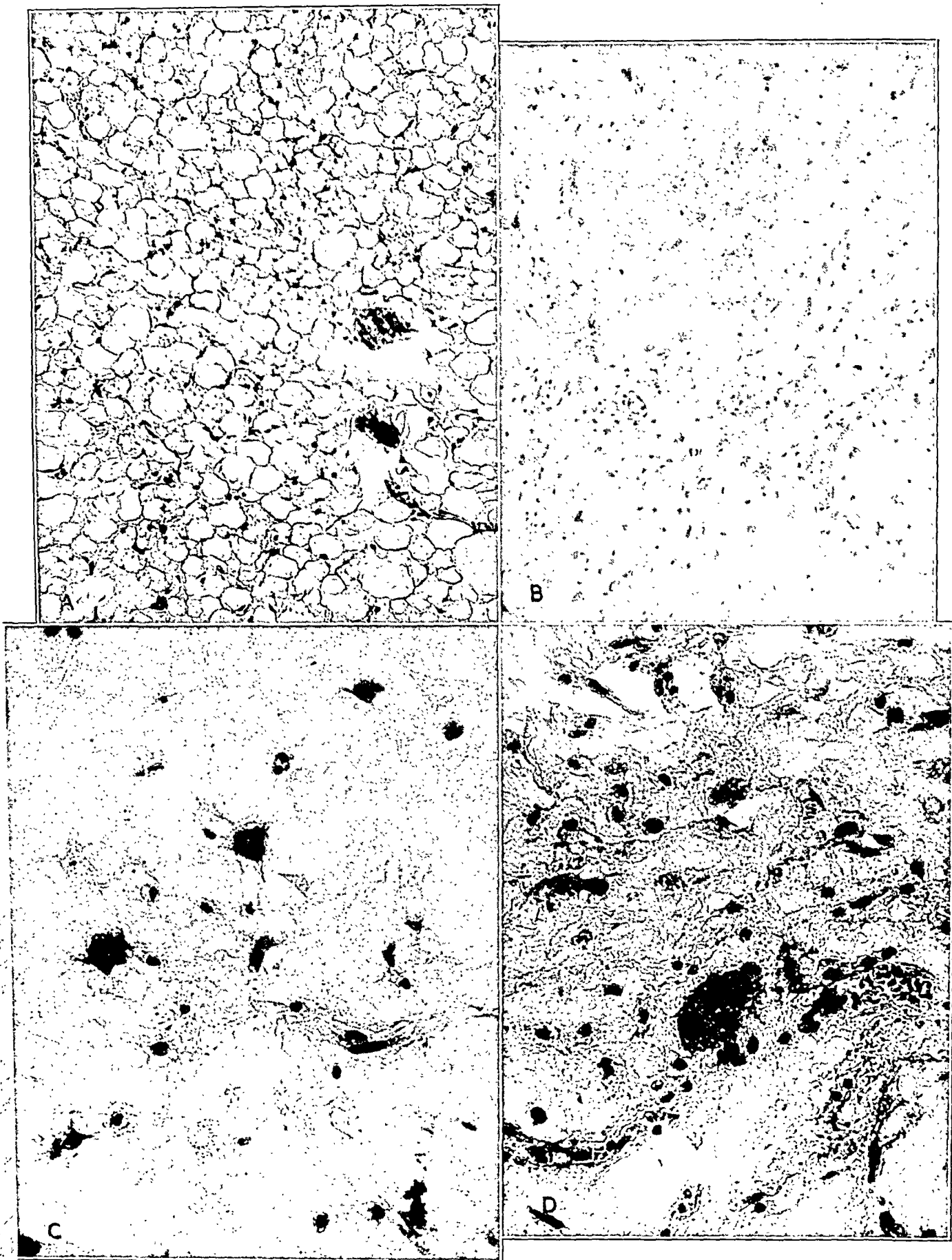


Fig. 4.—*A*, lipoma. Note the fat cells. Hematoxylin-eosin preparation; $\times 128$. *B*, myxomatous degeneration. Hematoxylin-eosin preparation; $\times 120$. *C*, myxomatous degeneration. Note the stellate cells with processes. Hematoxylin-eosin preparation; $\times 380$. *D*, lipoma with myxomatous degeneration and multinucleated cells. Hematoxylin-eosin preparation; $\times 380$.

weighed $9\frac{3}{4}$ pounds (4.4 Kg.). The pathologic diagnosis was fibromyxolipoma. A year previously a small lipoma had been removed from the shoulder.

Johnson¹⁰ reported a case of pure lipoma in a man. The tumor was on the right side; it weighed $10\frac{1}{2}$ pounds (4.7 Kg.).

Krogius¹¹ reported a case in which a lipoma weighing 6,150 Gm. was removed from a woman aged 51. The tumor was on the left side.

Pritzi¹² reported a case in a woman aged 62; the tumor was on the right side. Before operation there was a loss of function of the right kidney. After removal of the tumor, the renal function speedily returned to normal. There was a recurrence which originated from the left side and was so intimately attached to the kidney that the left kidney had to be removed. This demonstrated the desirability of having saved the right kidney at the first operation.

Mayo and Dixon¹³ reported 3 cases. The first occurred in a woman, aged 45, who was operated on for an "ovarian tumor" and in whom at operation a $17\frac{1}{2}$ pound (7.9 Kg.) retroperitoneal lipoma was found situated between the stomach and the colon. In the second case, there was an 18 pound (8.2 Kg.) fibromyxolipoma. The patient was operated on for a supposedly malignant condition. In the third case, the tumor was situated in the mesentery of the descending colon.

Burger¹⁴ reported a case in a man, aged 61, in which a preoperative diagnosis of right-sided benign retroperitoneal tumor was made. The chief complaint in this case had been the occurrence of jaundice at irregular intervals. At operation it was found that the tumor involved the right flank, pushed the cecum to the midline and extended through the femoral ring. Burger thought that the tumor may have originated in the thigh and pushed upward through the inguinal ring.

Hunt and Simon¹⁵ reported a case in a woman aged 49; the tumor was on the left side.

Katz¹⁶ reported 2 cases. In the first case, there was a fibrolipoma on the right side, which recurred one and a half years later. In the

10. Johnson, P. P.: Retroperitoneal Perirenal Lipoma. Boston M. & S. J. **189**:907 (Dec. 6) 1923.

11. Krogius, A.: Research on So-Called Retroperitoneal Lipomas, Finska läk.-sällsk. handl. **67**:833 (Oct.) 1925.

12. Pritzi, Otto: Retroperitoneal Tumors, Arch. f. klin. Chir. **140**:583, 1926.

13. Mayo, C. H., and Dixon, C. F.: Retroperitoneal Lipoma: Report of Three Cases, Minnesota Med. **10**:272 (May) 1927.

14. Burger, T. O.: Large Retroperitoneal Tumor, S. Clin. North America **7**:1285 (Oct.) 1927.

15. Hunt, V. C., and Simon, H. E.: Perirenal and Intrarenal Lipoma, Am. J. Surg. **4**:390 (April) 1928.

16. Katz, N.: Ueber retroperitoneale Lipome, Beitr. z. klin. Chir. **142**:864. 1928.

second case, there was a liposarcoma on the left side, which weighed 18 pounds. The patient was operated on again two and five years later.

Crabtree¹⁷ reported a case of pararenal lipoma with abdominal lipomatosis in a patient 60 years old. The preoperative diagnosis was retroperitoneal lipoma.

RÉSUMÉ

We have found many cases of retroperitoneal tumors reported in the literature, but have collected only those proved by excision and section to be lipomas or lipomas undergoing sarcomatous changes; in short, tumors of definite fatty origin. The recent cases do not bring out anything new or even materially change the statistics.

In summary, one might say that these tumors occur more frequently in women than in men, usually in the fourth or fifth decade. They arise most commonly from the perirenal fat. The most noteworthy feature is the absence of definite symptoms, as a rule, the chief complaint being the enlargement of the abdomen associated with vague abdominal discomfort. The symptoms are due entirely to pressure except in a few cases in which a loss of weight occurs apparently in surprising contrast to the enlargement of the abdomen.

The treatment is excision, which is sometimes easy and sometimes difficult. The chief difficulty usually lies in the freeing of the mesenteric vessels. Frequently one or another of the kidneys is so intimately engulfed in the mass that it must be removed. The desirability, however, of saving the kidney is demonstrated by Pritzi's case.¹²

There is a marked tendency for retroperitoneal lipomas to undergo sarcomatous change. Recurrences are not infrequent. Correct preoperative diagnosis is difficult, but in a few typical cases has been made. Roentgenograms are of great assistance in determining the origin of the tumor and renal tests in differentiating these tumors from polycystic kidney, hypernephroma or other renal tumors. Because of the possibility of having to remove the attached kidney at operation, renal function tests should always be made.

Our case demonstrates the feasibility of the transverse incision, which in this instance almost bisected the patient.

17. Crabtree, E. G.: Pararenal Lipoma with Generalized Abdominal Lipomatosis, *Tr. Am. A. Genito-Urin. Surg.* **22**:11, 1929; *J. Urol.* **23**:543 (May) 1930.

A RAPID METHOD OF PROTECTING THE PERITONEUM AGAINST PERITONITIS*

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The subject of peritonitis and especially its prevention by active immunity methods lately has aroused the interest of American investigators. The problem of active peritoneal immunity may be said to have been opened by Pfeiffer and Isaef¹ with their demonstration of bacterial lysis within the peritoneal cavity in immunized animals (Pfeiffer phenomenon). This lysis was shown by the authors to be humoral and produced by the bacteriolysins of the serum. The next step was made by Piérallini,² who found that a leukocytic exudate could be obtained in the peritoneal cavity by the injection of foreign substances, including physiologic solution of sodium chloride. He was followed by Garnier,³ who confirmed the presence of a leukocytic exudate in the peritoneal cavity of immunized animals, and found that bacteria are rapidly destroyed in the presence of such an exudate. Solieri⁴ definitely applied such immune responses to peritonitis. He produced a peritoneal leukocytic exudate, and found that the animals with such a hyperleukocytosis survived a colon bacillus peritonitis. The subject was reopened in this country by Goldblatt and me⁵ by the demonstration that intraperitoneal immunization by living and heat-killed colon bacilli induced an immu-

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* From the Laboratories and the Department of Medical Research of the Toledo Hospital.

* This work is a part of a general investigation on "Recovery in Peritonitis" aided in part by a grant by the Committee on Scientific Research of the American Medical Association.

1. Pfeiffer and Isaef: *Ztschr. f. Hyg. u. Infektionskr.*, 1894, vol. 17; *Deutsche med. Wchnschr.*, 1894, no. 13.

2. Piérallini, G.: *Sur la phagolyse dans la cavité péritonéale*, *Ann. Inst. Pasteur*, 1897, p. 308.

3. Garnier, M.: *Recherches sur la destruction des microbes dans la cavité péritonéale des cabayes immunisés*, *Ann. Inst. Pasteur* **11**:767, 1897.

4. Solieri, S.: *Experimentelle Untersuchungen über die Veränderungen des Widerstandes des Peritoneums gegen die Infektion durch Bacterium coli*, *Beitr. z. path. Anat. u. z. allg. Path.* **31**:536, 1902.

5. Steinberg, B., and Goldblatt, H.: *Active Immunization Against Experimental Peritonitis*, *Am. J. Path.* **3**:541, 1927.

nity to subsequent colon bacillus and fecal peritonitis. Later⁶ we emphasized the preferable use of dogs as experimental animals and pointed out⁷ that immunization with heat-killed colon bacilli was not as efficient as with living organisms. Herrmann⁸ used rabbits as experimental animals and adopted our method of producing fecal peritonitis in those animals. He found that immunization with a mixture of colon bacilli and streptococci was more efficient than with colon bacilli alone. Although his protocols show only a difference of 5 per cent between the two methods in the survival of animals, he expressed the belief that because of the survival of some of the controls, the animals immunized with colon bacilli did not have as severe peritonitis as rabbits immunized with the mixture. Rankin and Bargaen⁹ applied clinically the process of active immunization, and expressed their belief that it protects the patient from peritonitis.

This work was undertaken to determine the shortest time in which active immunity could be conferred on an animal so that it could survive an experimentally produced peritonitis. The immunizing agents consisted of heat-killed colon bacilli and a mixture of the colon bacillus, streptococcus, *Bacillus pyocyaneus*, enterococcus, *Bacillus mucosus-capsulatus* and *Bacillus welchii*. These bacteria were isolated from appendixes with appendicitis and were of a determined marked virulence. Dogs were used exclusively as experimental animals.

EXPERIMENTS

EXPERIMENT 1.—*Immunizing Injections of Heat-Killed Colon Bacilli Followed by Production of Peritonitis with the Colon Bacillus.*—One group of twelve animals was given a single intraperitoneal injection of 1 agar slant of *B. coli* (300) consisting of 1,000,000,000 organisms. The slant was washed off with physiologic solution of sodium chloride heated at 60 C. for forty-five minutes, and injected intraperitoneally. On the following day each animal of the group, as well as four normal control dogs, received intraperitoneally 3 slants of living *B. coli* (300) suspended in 2.5 per cent tragacanth, U. S. P., made up in saline. All the controls died in from seven and one-half to sixteen hours of hemorrhagic fibrinopurulent peritonitis. Ten of the twelve dogs that had received a single immunizing dose of *B. coli* died of fibrinopurulent peritonitis.

6. Goldblatt, H., and Steinberg, B.: Peritonitis: III. Active Immunization Against Experimental *B. Coli* Peritonitis, *Arch. Int. Med.* **41**:42 (Jan.) 1928.

7. Steinberg, B., and Goldblatt, H.: Peritonitis: IV. Production of Active Immunity Against the Fatal Outcome of Experimental Fecal Peritonitis, *Arch. Int. Med.* **42**:415 (Sept.) 1928.

8. Herrmann, Siegfried F.: Experimental Peritonitis and Peritoneal Immunity, *Arch. Surg.* **18**:2202 (May) 1929.

9. Rankin, F. W., and Bargaen, J. A.: Vaccination Against Peritonitis in Surgery of the Colon, *Arch. Surg.* **22**:98 (Jan.) 1931.

Another group of ten animals was given two intraperitoneal injections of heat-killed *B. coli*. The first injection consisted of 1 slant (1,000,000,000); the second injection was given on the following day and consisted of 2 slants (2,000,000,000) of *B. coli*. On the day following the second injection, the ten animals and four normal control dogs were given *B. coli* and tragacanth to produce peritonitis, as were the first group. The four controls died. Eight of the ten dogs which had received the injections died.

A third group of ten dogs was given three intraperitoneal injections of heat-killed *B. coli*. The first injection consisted of 1,000,000,000 organisms; the second injection on the following day, of 2,000,000,000 organisms, and the third injection on the third day, of 3,000,000,000 organisms. On the day after the third injection,

TABLE 1.—*Immunization of Dogs with Varying Amounts of Heat-Killed Colon Bacilli and Followed by Production of Peritonitis with B. Coli at Varying Intervals Following the Immunization*

Number of Dogs	Number of Injections	Number of Days Between First Immunizing Injection and Peritonitis	Number of Dogs Survived	Number of Dogs Died
12	1	1	2	10
10	2	2	2	8
10	3	3	1	9
28	4	4	18	10

TABLE 2.—*Immunization of Dogs with Four Successive Injections of Heat-Killed Colon Bacilli and Followed by Production of Peritonitis with B. Coli at Varying Intervals Following Immunization*

Number of Dogs	Number of Immunizing Injections	Number of Days Between First Immunizing Injection and Peritonitis	Number of Dogs Survived	Number of Dogs Died
28	4	4	18	10
9	4	8	6	3
9	4	17	9	0
10	4	27	8	2

peritonitis was produced with *B. coli* and tragacanth in the group of ten animals and four normal control dogs. All the controls died; nine of the ten dogs which had received the injections died.

A fourth group of twenty-eight dogs (in series of 10, 10 and 8) was given four intraperitoneal injections of heat-killed *B. coli*. The first injection consisted of 1,000,000,000 organisms; the second injection on the following day, of 2,000,000,000; the third injection on the next day, of 3,000,000,000, and the fourth injection on the fourth day, of 4,000,000,000 organisms. Peritonitis was produced with *B. coli* and tragacanth in six normal control dogs and in the twenty-eight dogs the day after the fourth injection. All the control dogs died. Of the twenty-eight dogs, ten died.

A fifth group of twenty-eight dogs was given four intraperitoneal injections of heat-killed colon bacilli as the fourth group. In nine of these animals, peritonitis was produced with the colon bacillus eight days after the first immunizing injection;

six survived and three died. In another set of nine animals, peritonitis was produced with the colon bacillus seventeen days after the first immunizing dose. All of them survived. In the last set of ten dogs, peritonitis was produced with the colon bacillus twenty-seven days after the first injection. Eight survived; two died. With each set of animals, a similar type of peritonitis was produced in two normal controls. All the controls died.

EXPERIMENT 2.—*Immunizing Injections with a Bacterial Mixture Followed by Peritonitis Produced with the Colon Bacillus.*—One group of twelve animals was given four intraperitoneal injections of a heat-killed bacterial mixture previously described in a manner similar to that given the fourth and the fifth group

TABLE 3.—*Difference in Survival Following Immunization with Heat-Killed B. Coli and Immunization with Bacterial Mixture Followed by Peritonitis Produced with Colon Bacillus*

Number of Dogs	Number of Immunizing Injections	Number of Days Between First Immunizing Injection and Onset of Peritonitis	Type of Immunizing Material	Number of Dogs Survived	Number of Dogs Died
28	4	4	Heat-killed B. coli	18	10
12	4	4	Heat-killed bacterial mixture	3	9

TABLE 4.—*Difference in Efficacy of Immunization with Colon Bacillus and Immunization with a Bacterial Mixture in Relation to Survival Following Peritonitis Produced with Colon Bacillus*

Number of Dogs	Number of Immunizing Injections	Number of Days Between First Immunizing Injection and Peritonitis	Type of Immunizing Material	Number of Dogs Survived	Number of Dogs Died
10	4	27	Heat-killed B. coli	8	2
10	4	27	Heat-killed mixture	6	4

in experiment 1. Since there were six different organisms, each injection contained an equal sixth of each bacterium. Four days after the first immunizing dose, peritonitis was produced with the colon bacillus in each of the twelve animals and three normal control dogs. The three control dogs died. Of the twelve dogs, nine died and three survived. Table 3 shows the difference in survival between the animals immunized with the mixture and those immunized with the colon bacillus (experiment 1, group 4).

Another group of ten animals was given four intraperitoneal injections of a heat-killed bacterial mixture in the same manner as were the first group in the experiment. Twenty-seven days after the first immunizing dose, peritonitis was produced with the colon bacillus in the ten animals and in two normal control dogs. The control dogs died. Of the ten immunized animals, six survived and four died. Table 4 shows the difference in survival between animals immunized with the mixture and those immunized with colon bacillus (the final set of the

fifth group of experiment 1) after a period of twenty-seven days following the first immunizing injection.

EXPERIMENT 3.—*Immunizing Injections with Heat-Killed Colon Bacilli or with Bacterial Mixture Followed by a Peritonitis Produced by Injecting Intraperitoneally Three Slants of the Bacterial Mixture Suspended in Tragacanth.*—A group of ten animals was given four intraperitoneal injections of heat-killed colon bacilli as in the previous experiments. Another group of nine animals was given four intraperitoneal injections of a bacterial mixture. In the nineteen experimental animals and five normal control dogs, peritonitis was produced by injecting a bacterial mixture four days after the first immunizing dose. All of the control dogs died. Of the ten dogs immunized with colon bacilli, three survived and seven died. Of the nine dogs immunized with the mixture, two survived and seven died.

TABLE 5.—*Immunization of Dogs with Heat-Killed Colon Bacilli or a Mixture of Bacteria Followed by Production of Peritonitis with Bacterial Mixture Four Days After the First Immunizing Dose*

Number of Dogs	Number of Immunizing Injections	Kind of Immunizing Material Used	Number of Dogs Survived	Number of Dogs Died
10	4	Heat-killed <i>B. coli</i>	3	7
9	4	Heat-killed mixture of bacteria	2	7

TABLE 6.—*Difference in Percentage of Survivals of Animals Protected with Colon Bacillus and Animals Protected with Bacterial Mixture*

Percentage of Survivals	Method of Immunization	Type of Peritonitis Produced
65	Heat-killed colon bacilli	Colon bacillus
25	Heat-killed bacterial mixture	Colon bacillus
30	Heat-killed colon bacilli	Bacterial mixture
22	Heat-killed bacterial mixture	Bacterial mixture

COMMENT

From these experiments, it is apparent that some type of immunity is established by the intraperitoneal introduction of heat-killed bacteria. It is also apparent that the type of the colon bacillus (300) that I used (this organism has been used in all the previous experiments) is capable of establishing a higher degree of immunity than a mixture of virulent organisms most frequently found to be associated with appendicitis and peritonitis. A slight degree of protection is established following only one intraperitoneal injection when peritonitis is produced on the following day. The material used to produce peritonitis is from three to five times the lethal dose for a dog weighing from 10 to 15 Kg. If it were possible to grade the degree of peritonitis, it is very likely that even a greater percentage of survivals would have been obtained. The determination of agglutinins and the bactericidal power of the serum and of the peritoneal exudate following one, two, three and four peri-

toneal immunizing injections failed to reveal the presence of humoral antibodies (some of the dogs that were given four injections had an agglutinin titer of 1:100 or of 1:200) to account for this immunity. In a previous publication, Snyder and I¹⁰ showed that an animal given time to establish immunity responds to peritonitis by a rapid and extensive polymorphonuclear mobilization and a rapid phagocytosis. The phagocytosis was found to be nonspecific; the polymorphonuclears

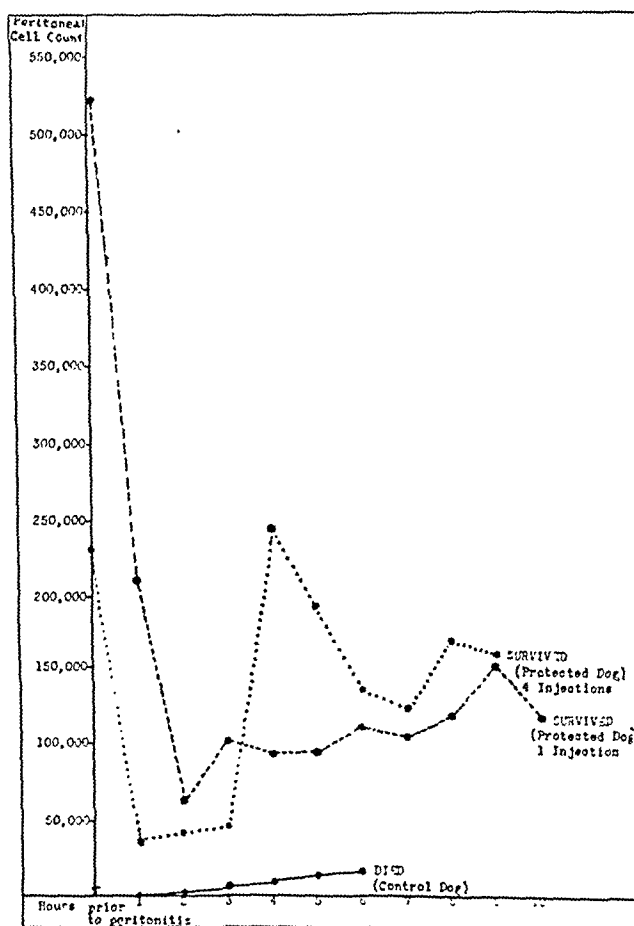


Chart 1.—Leukocyte counts per cubic millimeter of peritoneal exudate during the course of a colon bacillus peritonitis in a normal control dog, in an animal that had received one protecting bacterial injection and in another animal that had received four injections. Notice the marked difference in the cellular response between a normal and a protected dog.

evoked by immunization with colon bacillus phagocytosed indiscriminately all types of bacteria in the peritoneal exudate produced by fecal material.

Since humoral antibodies were not present, a study of the peritoneal exudate of the animals with a single, two, three and four immu-

10. Steinberg, B., and Snyder, D.: Immune Cellular Reactions in Experimental Acute Peritonitis, *Arch. Path.* 8:419 (Sept.) 1929.

izing injections was made. The methods employed were those described by Snyder and me. Prior to the production of peritonitis, peritoneal and peripheral blood cell and differential counts were made. After the production of peritonitis, in addition to hourly peripheral and peritoneal cell counts, bacterial counts of the peritoneal exudate were made. The exudate was secured by puncturing, under sterile precautions, the abdominal wall with a capillary glass pipet.

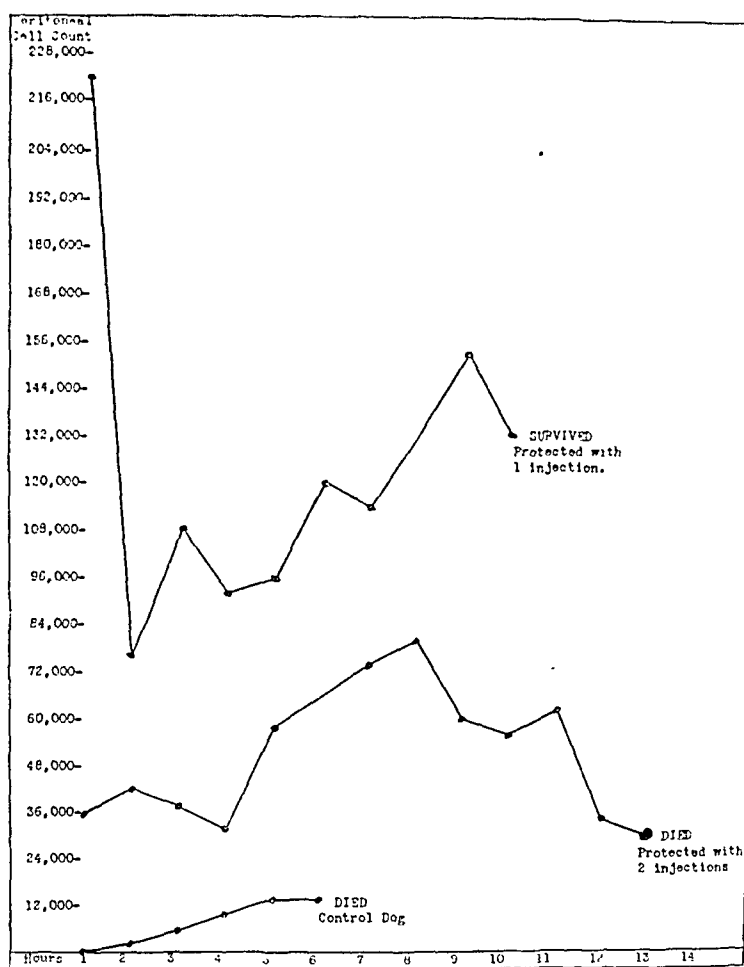


Chart 2.—Leukocyte counts per cubic millimeter of peritoneal exudate during the course of a colon bacillus peritonitis in a normal control dog, in a presumably protected animal that died and in a protected animal that survived. Observe the higher counts in the surviving animal, although it received one less protecting injection than the animal that succumbed.

Chart 1 shows the comparison of the peritoneal cell counts in cubic millimeters of exudate of a normal control dog with peritonitis, an animal given one and another animal four immunizing injections followed by the production of peritonitis with the colon bacillus. The animals with protecting injections have a decidedly greater number of cells in the peritoneal exudate. Chart 2 shows the difference between two ani-

imals; each had been given immunizing injections, but one died and the other survived following peritonitis produced by the colon bacillus. The surviving animal had a decidedly and consistently greater cellular peritoneal content than the animal that died, though the latter had

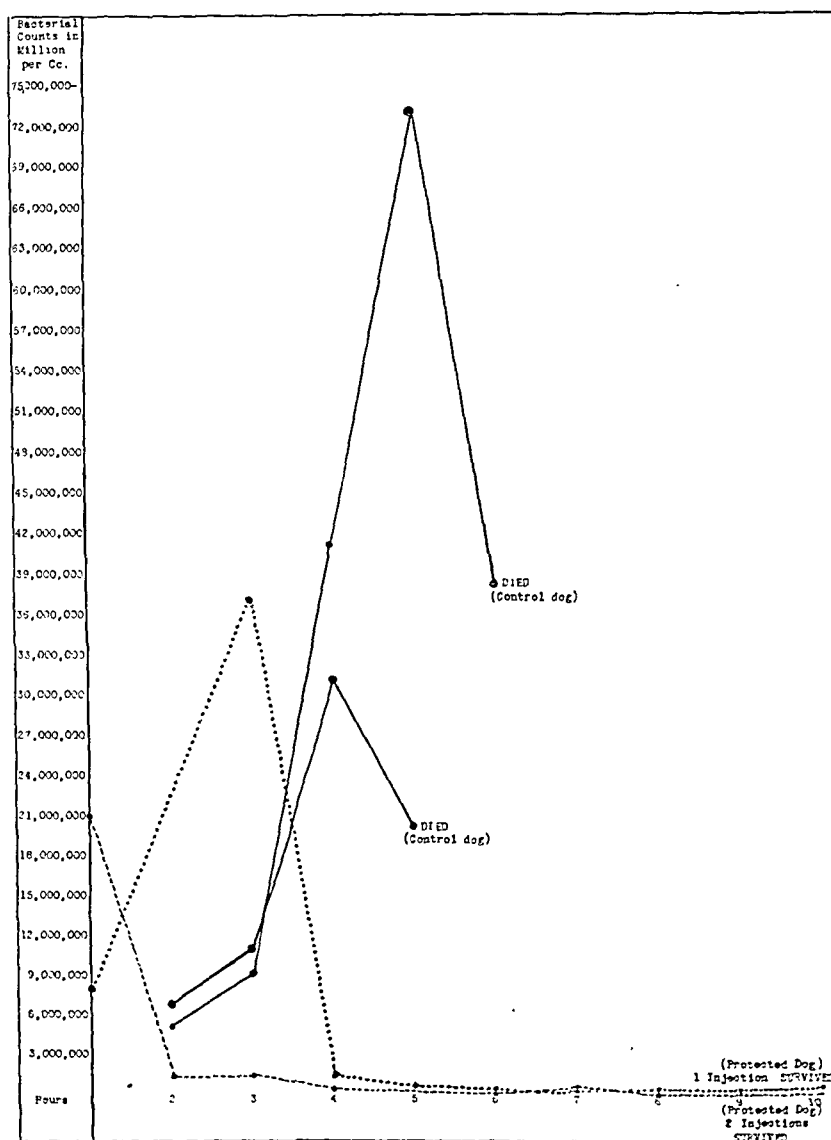


Chart 3.—Bacterial counts per cubic centimeter of peritoneal exudate during the course of a colon bacillus peritonitis in normal control dogs and in protected dogs. Observe the high bacterial counts in the normal dogs and the very low counts in protected dogs. Since the method of counting bacteria included the phagocytosed as well as the free bacteria, it is assumed that these counts represent the total number of all viable bacteria present in the peritoneal cavity.

received one more immunizing injection than the surviving animal. Chart 3 shows the difference in the bacterial counts of two normal control dogs and two animals that had received immunizing injections dur-

ing the course of a peritonitis due to the colon bacillus. It is apparent that in the normal control dogs the number of bacteria gradually rise during the first five hours and remain in large numbers until the animal dies. On the other hand, the dogs that received immunizing injections revealed a gradually diminishing number of bacteria. The contrast in the bacterial content of the normal control and the immune animals is striking.

Hourly examination of the peritoneal smears revealed complete phagocytosis in the protected animals within four hours, while smears from the normal control dog contained large numbers of bacteria throughout the course of the peritonitis. Since the bacteria are found phagocytosed within polymorphonuclears in the protected dogs and the bacteria show diminishing numbers, it may be assumed that either the bacteria are destroyed by the polymorphonuclears in situ or else the bacteria-laden polymorphonuclear cells migrate to other parts of the body. Three factors favor the conception of migration of leukocytes: 1. The ebb and rise of the cellular content in the peritoneal exudate (chart 2) suggest that the variation in number may be due to migration of old cells followed by a substitution by newly evoked cells. 2. The peritoneal smears do not reveal breaking up of bacterial bodies outside or within polymorphonuclears. 3. Bacteria are capable of surviving within a leukocyte for many days, as was demonstrated by Metchnikoff. The migration conception is further strengthened by experiments to be reported later in which the polymorphonuclears of immunized animals that died were traced from the peritoneal cavity.

It is apparent that in animals given a few immunizing injections and in which peritonitis is produced the following day the protecting mechanism cannot be considered either a humoral or a cellular immunity in the accepted sense. It may be said that the animals survive because phagocytes (polymorphonuclears) happen to be present in the particular locality in which the infection occurs. That the initial process is essentially and primarily that of phagocytosis is evident from these experiments. Such a process can hardly be classified as a local type of immunity, and I suggest the term "hyperleukocytic pre-immunity".

APPLICATION OF THE PERITONEAL HYPERLEUKOCYTIC PRE-IMMUNITY TO MAN

Within the last two years, seventeen persons had been immunized by intraperitoneal injections of heat-killed colon bacilli prior to abdominal operations. These operations consisted of resection of the colon, intestinal anastomosis, old endometriosis with obstruction of the bowel and old appendical abscess. The immunizing material was given intraperi-

toneally daily on four successive days, and operation was done on the day following the last protecting dose. At present the protecting material consists of 50 cc. of physiologic solution of sodium chloride in which are suspended 4,000,000,000 colon bacilli (culture 300). The material is heated at 60 C. for forty-five minutes and made up to volume. After the determination of the absence of viable organisms the following doses are given: first day, 5 cc.; second day, 10 cc.; third day, 15 cc.; fourth day, 20 cc. The comparatively large amount of fluid allows the spread of the protecting material throughout the peritoneal cavity. At operation, the peritoneum shows a purulent peritonitis. The reactions experienced are slight and correspond to a mild peritonitis. All the patients made an uneventful recovery. Naturally, no conclusions regarding the merit of the procedure could be drawn from such a clinical application without properly controlled animal experimentation, which constitutes the only reliable criterion. At the present time, experiments are being undertaken to apply such peritoneal protection in acute and subacute pelvic inflammatory conditions.

SUMMARY

1. Protection against peritonitis can be obtained by the intraperitoneal injection of colon bacilli (culture 300).
2. Protection secured with heat-killed colon bacilli is greater than that obtained with a mixture of the virulent organisms usually found in appendicitis and peritonitis.
3. The protection secured is not a true immunity process, but a hyperleukocytosis and phagocytosis due to a coincident presence of polymorphonuclears at the site of infection. The term hyperleukocytic preimmunity is suggested for this process.
4. By means of these experiments on animals, a method is introduced that is applicable in the prevention of peritonitis in man following surgical intervention in the intestinal tract.
5. The protection can be achieved in four days, allowing the performance of the operation on the fourth or the fifth day after the first immunizing dose.

THE TREATMENT OF INTUSSUSCEPTION

REPORT OF A CASE WITH PERFORATION *

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The treatment for intussusception is primarily surgical. The surgical procedure involved is determined by the condition of the bowel as found at the time of the operation. Ordinarily, this condition depends on the time elapsing between the formation of the intussusception and the operation. Consequently, an early diagnosis becomes an important part of the treatment, since a relatively simple operation with the patient in good condition is usually the result.

DIAGNOSIS

There are two procedures of decided value in the diagnosis to which I wish to call attention. If an intussusception is suspected but not felt, either because of the abdominal distention or because of the child's crying, the following procedure will often result in a positive diagnosis. The examiner's right index finger is placed in the child's rectum and his left hand on the abdomen. The assistant then holds the child in a sitting posture with its face toward the examiner. The tumor will usually drop down between the examiner's hands.

When the diagnosis is not certain, or if it is made and the position of the lesion not located, roentgen examination is advisable. When the condition of the patient calls for as little loss of time as possible, a roentgenogram of the abdomen made without any preparation will often show the distended loops above the lesion and indicate the position of the intussusception by the difference in the shadow of the large and small intestine.

Le Wald¹ has demonstrated graphically the value of the barium enema in the diagnosis of intussusception when the patient's condition permits. If the obstruction is complete, the site will be shown. If it is incomplete, the enema will show the constriction and may show where the barium filters around the invagination and remains after the enema has been expelled from the bowel.

* Submitted for publication, May 19, 1931.

* From the surgical service of St. Luke's Hospital.

1. Le Wald, L. T.: *Johnson's Operative Therapeutics*, New York, D. Appleton and Company, 1915, vol. 4, chapt. 3, p. 208; personal communications.

REDUCTION

Nonoperative Reduction.—The reduction of an intussusception may be nonsurgical, accomplished by the use of pressure enemas or air insufflation; but if this method is successful, it should be followed by abdominal exploration to make certain that reduction is complete and that there is no gangrene, perforation or tumor present. Both Farr² and Montgomery³ recommend the aid of air insufflation of the colon in the reduction of all intussusceptions at the time of operation. This simplifies the locating of the lesion, reduces the less severe ones without handling of the intestine other than for exploration and makes possible reduction in some of the advanced cases in which the intussusception otherwise might not be reducible. The procedure should at all times be under visible control. The air empties readily from the rectum.

Operative Reduction.—A small, early intussusception is easily reduced, and the operative procedure is completed. Also many of the larger, later and consequently more edematous intussusceptions may be reduced. Careful manipulation is necessary, as the tissues are very friable. Gentle stripping, rolling or milking back of the intussusciens while constant but gentle backward pressure is maintained on the apex of the intussusceptum will usually bring about reduction. McGlannan⁴ stated that a flat blunt dissector or the handle of the knife introduced inside of the neck may aid the reduction. If the intussusception is wrapped in moist gauze, and even, steady pressure applied for a few minutes, with great care, the edema may be so relieved that reduction becomes possible.

The intestines should at all times be protected with gauze saturated with warm physiologic solution of sodium chloride, and they should be kept within the abdominal cavity as much as the operative procedures will permit. Cheever⁵ advises that, if greatly distended, the intestine be eviscerated into a moist rubber dam bag kept warm by hot compresses to its exterior surface, provided that the distended loops prevent the necessary exploration or operative procedures.

TYPES OF INTUSSUSCEPTION

Irreducible Intussusception.—Some cases will be found in which reduction cannot be accomplished. Formerly, it was the practice of

2. Farr, C. E.: The Reduction of Colonic Intussusception by Air Inflation, *Ann. Surg.* **84**:588 (Oct.) 1926.

3. Montgomery, A. H.: Intussusception and Some other Surgical Conditions of the Abdomen in Children, *Nebraska M. J.* **15**:21 (Jan.) 1930.

4. McGlannan, Alexius, in Lewis: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, 1929, vol. 7, chapt. 4, p. 22.

5. Cheever, David, quoted by Hartwell and Cooper, in Lewis: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, 1929, vol. 7, chapt. 7, p. 33.

many surgeons in this type of case to incise the bowel at the point of invagination, reduce the intussusception and close the opening thus made. A simple and effective method for making the incision is described by Brown.⁶ One blade of the scissors is inserted under the edge of the neck of the intussusception, and the neck is cut across parallel to the long axis of the intestine.

For irreducible intussusception in children, not complicated by gangrene, McGlannan⁴ advises enterostomy above the lesion when one-stage resection is contraindicated by the patient's condition. He stated that this may be followed by spontaneous reduction, and feels that multiple stage resections in children do not give good results. Of course, should reduction not occur following the first operation, a second operation for the purpose of reducing or resecting the intussusception would be necessary.

Others drop the intussusception back into the abdomen and do a lateral anastomosis between the afferent and efferent loops of intestine; for example, in an intussusception at the ileocecal valve, an anastomosis is made between the terminal ileum and the ascending or transverse colon. To this procedure Montgomery⁷ has added a fixation of the invagination by 'placing a few interrupted sutures through the serosa and muscularis of the two portions of the intussusception at its point of entrance. This prevents leakage as the invaginated portion sloughs off.

Gangrenous Intussusception.—At times the pressure on the invaginated blood vessels has been great enough and has existed sufficiently long for the intestinal wall to become gangrenous. If this condition is diagnosed before reduction is accomplished, the logical treatment would be by one of the methods just described. But, when the condition is found after reduction, removal of the involved portion is indicated.

A resection followed by a lateral anastomosis is the ideal operation. In most cases the condition of the patient, usually an infant, will not justify the time necessary for the operation and the manipulation involved. A "double-barrel" resection is a life-saving procedure under such circumstances. The involved loop is brought out through a second incision, but if the patient's condition is critical, the loop may be brought out through the original incision. A few sutures will hold the "barrels" together. A drain is placed in the peritoneal cavity, and the wounds are closed.

6. Brown, H. P., Jr.: Acute Intussusception in Children, *Ann. Surg.* **81**:637, 1925.

7. Montgomery, A. H., and Mussil, J. J.: The Treatment of Irreducible Intussusception in Children, *Surg., Gynec. & Obst.* **51**:415 (Sept.) 1930.

An "extra-abdominal" ileostomy is then done in the following manner.

A number 16 soft rubber catheter is inserted into the proximal end of the intestine just distal to its emergence from the incision and held in place with a purse-string suture. The catheter should extend several inches into the intestine.

The loop is clamped off with one or two large clamps, and cut away at once with the cautery. The clamps are left on until there is necrosis of the end of the intestine and leakage occurs. This is usually on the fourth or fifth day. In the meantime, the wound is protected and the obstruction is relieved by the catheter. When healing occurs, a clamp is put on with a jaw in each end of the intestine, and by pressure necrosis the lumina of the two ends are joined. This should be done as deeply as possible to insure a large connection. Later a closure is done by the intraperitoneal or the extraperitoneal method, whichever is indicated.

Perforation.—To the gangrenous intussusception may be added the complication of perforation. When gangrene does develop, it is ordinarily in the portion of the intussusception that is within the intestinal lumen, so that perforation does not necessarily soil the peritoneal cavity. However, by pressure closing the vessels to the wall of the intussusciens or by direct pressure of the intussusception against the intussusciens, a small area of necrosis with resulting perforation into the peritoneal cavity may result. This is the condition that was found in the case reported in this paper.

The ideal treatment would be closure of the small perforation by two purse-string sutures, or, if the intestine is gangrenous, resection and lateral anastomosis with drainage of the peritoneal cavity. But in these cases, even more so than in any of the types already considered, a brief operation with the least possible trauma is indicated. As perforations are not to be expected in the cases that are readily reduced and show no other damage to the intestinal wall, the treatment in such cases need not be considered here.

Once more, the quickest procedure that will remove the damaged intestine, relieve the obstruction and care for the soiled peritoneum is the modified Mikulicz operation, which has just been described. Time will be saved by bringing the loop out through the original incision. Adequate drainage should be established by the insertion of rubber dam drains.

ADDITIONAL TREATMENT

The procedure in all operations for intussusception must include a careful palpation for a tumor in the intestine as a possible cause for the condition. Such tumors have been reported as multiple in some cases, even causing a later second intussusception. If found, the tumor should be removed by whatever type of operation its nature and the patient's condition dictate.

As to an anesthetic, ether will usually be found best suited to the needs. The required manipulations are very difficult to do on an infant, or even on a child, under local anesthesia.

Preoperative preparation should include the administration of water, salt and dextrose by hypodermoclysis or infusion. If indicated, the stomach should be lavaged. A patient in poor condition may be carried through the operation by a preoperative blood transfusion.

Immediate postoperative treatment for shock by intravenous injection of a saline solution, by blood transfusion or by both is often indicated, and will save many patients. Later, attention should be given to the maintenance of the fluid and salt balance and of nutrition, as indicated by the continuation of these measures plus hypodermoclysis.

When an enterostomy has been done, the catheter is irrigated with physiologic solution of sodium chloride or sodium bicarbonate solution every one or two hours and allowed to drain the remainder of the time. This prevents stoppage and possibly adds to the patient's fluid intake.

If resection has been done by the Mikulicz method, the skin about the wound is protected for the first four or five days by leaving the clamps in place and allowing drainage to take place through the catheter. When the clamps no longer hold, the skin is protected by the use of a paste made of kaolin and glycerin or by the use of tenth-normal hydrochloric acid and 10 per cent peptone solution. These solutions are introduced at half-hour or hourly intervals through a perforated tube incorporated in the dressing and encircling the ends of the intestine. Whatever excoriation does occur will be found to clear up rapidly as soon as the lumina of the ends of the intestine are united.

If the patient is an infant, particular emphasis should be placed on every possible effort being made toward getting the child out of the hospital at the earliest possible moment. The reason for this is self-evident when the effect of hospitalization on the normal infant is seen.

There is one more point to be noted in passing, which is an old story to the surgeon who has had a large number of these cases. An appendix delivered from an intussusception is so distended by the passive congestion that at first glance it may look as though the patient had acute appendicitis. It is very unwise to add an unnecessary appendectomy to a situation already precarious.

REPORT OF A CASE

History.—T. T., a boy, aged 15 months, was first seen in the pediatric dispensary at St. Luke's Hospital, on Oct. 8, 1930. Two days before, he had had diarrhea—foul mucus stools—with nausea and frequent vomiting. There had been some blood in an enema return, which the mother thought due to trauma.

The child was put on a regimen of forced fluids and sent home. On October 10 he was brought back to the clinic for reexamination. He had continued to vomit, and his abdomen was moderately distended. There had been no bowel movement,

but an enema had returned brown flakes and mucus with some flatus. As he appeared sick, although he had no fever and his blood count was normal, he was admitted to the hospital to the pediatric service.

October 11: The child continued to vomit, but did not look very sick. An enema returned a small amount of brown material and mucus. At one time when he was quiet, an indefinite mass was felt under the edge of the liver.

October 12: The child appeared sicker. The leukocyte count had doubled, being 12,200, with polymorphonuclears, 60 per cent, and lymphocytes, 40 per cent. Tenderness and rigidity had developed in the right side of the abdomen. Enemas gave no results except flatus in small amounts.

A surgical consultation was then asked for. When a rectal examination was made with the patient held in the sitting position, a mass dropped down between the examining fingers and the examiner's other hand.

Operation was done at once, with a diagnosis of chronic intussusception, which had developed acute signs in the right side of the abdomen.

Pathologic Findings.—The peritoneal cavity contained a considerable amount of serosanguineous fluid. The entire small intestine was greatly distended. At the ileocecal junction there was an intussusception forming a sausage-shaped mass nearly 6 inches (15.24 cm.) in length. This was located well up under the edge of the liver.

The right lumbar gutter contained fecal material and thin seropurulent fluid. In the cecum were two perforations the size of a finger-tip. The invaginated ileum was gangrenous, and on the adjacent loops of intestine there was a considerable deposit of fibrin.

Operative Procedure.—Under ether anesthesia, a rectus incision was made to the right of the umbilicus. The intussusception was located with considerable difficulty, but could be delivered into the incision. The terminal ileum proximal to the gangrenous intestine and the ascending colon distal to the perforations in the cecum were approximated with four interrupted chromic catgut sutures. A through-and-through suture was placed at each end of the incision; a small soft rubber dam drain was placed on each side of the loop of intestine, the upper into the right lumbar gutter and the lower into the pelvis. The loop of intestine was clamped and cut away with the cautery. This loop included the cecum, the appendix and the terminal 10 inches (25.4 cm.) of ileum. A number 16 soft rubber catheter was placed in the protruding end of the ileum and held in place with a purse-string suture. Foul brown fluid ran from the tube as soon as it was introduced.

Postoperative Course.—Immediately after operation, an infusion of 400 cc. was given, followed by a transfusion of 200 cc. of whole blood from the mother. Following this, the child's condition was fair.

Hypodermoclysis of 300 cc. of saline solution was given every eight hours until the end of the second day. It was then given only twice daily, as the child took fluids freely without nausea. The catheter was irrigated with physiologic solution of sodium chloride every hour.

The child's temperature remained between 104 and 105 F., and on the third postoperative day, he was given another transfusion of 200 cc. of whole blood from the mother to maintain nutrition.

Beginning on the fourth day the temperature declined, and by the sixth day was normal.

The clamps came away on the fourth day, and on the eighth day a Mikulicz clamp was applied to the two ends of the intestine. The next day the child's

temperature was 104 F. He looked sicker, and another transfusion of 200 cc. of whole blood was given.

His general condition improved gradually, the temperature dropped to normal, and on the eleventh day fecal material was passed by rectum. On the twelfth day, the clamp had cut entirely through.

As the opening between the two loops appeared to be too small, the Mikulicz clamp was reapplied, but gave a very inadequate opening. Consequently, two Kocher clamps were applied. This was an unfortunate measure, as the lateral clamp caused a perforation of the intestine that night. Stab wound drainage was instituted in the right flank, and in two days the temperature had returned from 105 F. to normal.

Convalescence continued uneventfully from that time. The drainage wound closed, the opening into the intestine became smaller gradually, and the child passed a normally formed stool every day. His strength and general condition improved steadily.

At the end of the tenth week he began to cough, and a white blood count of 129,000 developed, with polymorphonuclear leukocytes, 28 per cent, and lymphocytes, 72 per cent. By the next day this proved to be a definite and very severe case of whooping cough. Notwithstanding intensive treatment with vaccine and deep roentgen therapy, the child died one week after the onset of the disease.

SUMMARY

A detailed outline of the treatment for intussusception, particularly of the more severe types, is given.

A case of intussusception is reported which occurred in a child 15 months of age. In this case the intussusception had perforated, was irreducible and gangrenous. It was treated by a modified Mikulicz resection, with drainage of the peritoneal cavity. The child was apparently well on the road to permanent recovery when, in the eleventh postoperative week, he contracted whooping cough, from which he died three months after the original operation.

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FORTY-SIXTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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(Concluded from p. 170)

SYMPATHETIC NERVOUS SYSTEM

Sympathetic Ramisection.—Royle²⁶ made a study of the results obtained by the operation of sympathetic ramisection, basing his conclusions on a questionnaire sent to each of his patients, to which he received 126 replies, and on his records of the remainder of the 600 patients on whom he had performed the operation. There were three deaths, giving a mortality rate of 0.5 per cent. He tabulated the results according to the patients' answers as follows:

Congenital spastic paraplegia. Some benefit was obtained in 88 per cent of all patients, and good or excellent results in 75.6 per cent.

Congenital spastic hemiplegia. Some benefit was obtained in 97 per cent, and excellent or good results in 71.4 per cent.

Congenital spastic chorea. Some benefit was obtained in 100 per cent, and excellent or good results in 70 per cent.

Acquired spastic hemiplegia. Some benefit was obtained in 94 per cent, and excellent or good results in 58 per cent. Since a more complete

26. Royle, N. D.: *Canad. M. A. J.* **24**:229, 1931.

operation had been employed, including a thoracic sympathetic resection, the results were better.

Acquired spastic paraplegia, including disseminated or lateral sclerosis. Excellent or good results were obtained in all cases, but the numbers were too small to be reliable.

Parkinsonian rigidity. Some benefit was obtained in 68 per cent, and excellent results in 27 per cent.

Chronic constipation and megacolon. Excellent or good results were obtained in 100 per cent in each class of disease.

Raynaud's and Buerger's disease. Excellent or good results were obtained in 100 per cent of the patients with Raynaud's disease, and in 66 per cent with Buerger's disease.

Other conditions in which the operation had been performed were writer's cramp, sarcoma of the femur (for pain), anterior poliomyelitis, conditions simulating tic douloureux, unusual vasospastic conditions and retinitis pigmentosa.

The reports of other observers, however, have been less favorable as to the results of sympathetic ramisection. Thus Herz²⁷ studied the end-results in thirty-six patients, of whom thirty-two had been operated on by Royle himself. In nineteen cases the operation had been performed because of Little's disease. Of particular importance in evaluating the results were those patients in whom the operation had been done on one side only. Herz considered that the results in all cases were nil.

[ED. NOTE.—A vast amount of study, both experimental and clinical, has been devoted to the sympathetic nervous system in the last few years, and the physiologic effects of excision of parts of the sympathetic nerve chain in the different regions have been measured. The evidence has tended to show that the chief effects are an improvement in the circulation of an extremity due to vascular dilatation. It is probable that whatever improvement has been obtained by the operation in spastic paralytic conditions, and many observers dispute the claim of any improvement, has resulted from the increased blood supply.]

MISCELLANEOUS

Effects of Physical Therapy on Function and Structure.—Wolfson²⁸ summarized the results of studies made in the laboratories of Northwestern University Medical School of the effects of physical therapeutic procedures on the blood flow of a normal limb. Heat produced

27. Herz, M.: *Zentralbl. f. Chir.* 57:78, 1930.

28. Wolfson, H.: *Studies on Effect of Physical Therapeutic Procedures on Function and Structure: Effect of Blood Flow in Normal Limb*, J. A. M. A. 96: 2019 (June 13) 1931.

an increased blood supply due to active dilatation of the blood vessels. Massage and passive motion by mechanically emptying the blood vessels caused a temporary increase in the rate flow. Electricity, as applied, was effective in increasing the blood flow; its value in the treatment for poliomyelitis and peripheral nerve injuries might be due to some other effects not studied in these experiments. The suggestion was made to use more frequent but shorter treatments of massage and passive motion.

Volkman's Ischemic Contracture in Hemophilia.—An interesting case of Volkman's contracture developing following a hemorrhage in the arm in a patient with hemophilia, aged 8 years, was reported by Pasquali.²⁹ No bandage or splint had been used. He pointed out the medicolegal significance of the case as proving that ischemic contracture might develop in the entire absence of any external dressing.

Traumatic Lipo-Arthritis of Knee.—Under the name of lipoarthritis, Diamant-Berger and Sicard³⁰ studied the reactions provoked by trauma in the periarticular fatty tissues of the knee. From a review of the literature and after anatomic and physiologic investigations, they divided the physiopathologic manifestations into three types: one in which the lesion was localized to the infrapatellar fat pad (Hoffa's disease); a second in which the lesion was confined to a synovial fringe or solitary lipoma, the extracapsular lipoma of Lancereaux, and a third type that was generalized corresponding to the lipoma arborescens or the intracapsular lipoma of Lancereaux.

Hoffa's disease was always of traumatic origin, although this might be a single severe injury or several slight injuries. One found the infrapatellar fat pad hyperplastic and of a fibrous consistency, and on microscopic examination there was evidence of a subacute inflammatory reaction. The patient complained of pain localized to the anterior and medial part of the joint, aggravated by walking and worse at the moment of complete extension of the knee. These symptoms were sometimes accompanied by sensations of pinching in the joint, although less distinct than the locking caused by a loose body. Examination disclosed peripatellar swelling, readily palpable and giving the impression of fluctuation. Motions of the knee were free and painless except on extreme extension.

In the second type of lesion or solitary lipoma a history of an initial trauma was usually obtained. At arthrotomy one found a mass, either single or lobulated, attached by a pedicle of greater or lesser length, situated in one of the parapatellar culdesacs. The symptoms

29. Pasquali, E.: *Chir. d. org. di movimento* **15**:465, 1931.

30. Diamant-Berger, L., and Sicard, A.: *Rev. d'orthop.* **18**:5, 1931.

were those of a chronic posttraumatic synovitis with a localized area of pain, and accompanied by sudden sharp aggravations of pain and symptoms of locking. Synovial effusion commonly accompanied this lesion, whereas it was usually absent in the previous type. The authors called attention to the fact that these lipomas might develop torsion of their pedicles, and reported a typical instance.

The history of trauma in the third or generalized form was less clear, and sometimes it seemed to develop spontaneously. The finding at arthrotomy was a marked villus arthritis. The symptoms were those of a chronic hydro-arthritis, resistant to treatment and tending to recur.

The treatment varied according to the type of the lesion. In the localized infrapatellar fat pad lesion it was always worth while to try conservative measures in the beginning. The only operative treatment was total extirpation of the infrapatellar fat pad through a unilateral or bilateral parapatellar incision. In the solitary lipoma type of lesion operative removal ought to be advised. On the other hand, in the generalized form the advisability of operation was to be debated. One ought to try conservative treatment first, and it was only in case of complete failure that one would advise synovectomy.

Pellegrini-Stieda's Disease.—A very comprehensive discussion of the common metatraumatic ossification revealed by roentgen examination in relation to the internal femoral condyle of the knee was published by R. Petrignani.³¹ Usually associated with the name of Stieda, the author found it more exact to employ the name of its real discoverer, Pellegrini, whose publication preceded that of Stieda by two years. The bony formation was always of traumatic origin. It was found more frequently in men between the ages of 25 and 40 years and in laboring men or those engaged in athletics. The traumatism might be a direct contusion, indirect as a result of muscular contraction, or sprain, or a mixture of both sprain and contusion. In certain of the cases there was produced a fracture of the epicondyle, in others an avulsion of a small fragment of bone, and this was followed by ossification. In still others, and probably this was the more common mechanism, ossification developed in the fibrous covering of the epicondyle by a process of metaplasia after absorption of the hematoma produced by the trauma.

The symptoms associated with the lesion were variable, slight pain at the moment of injury being the chief sign, followed sometimes by functional weakness of varying severity. Swelling and heat were sometimes found on examination. Frequently there were no symptoms, and the patient sought advice only because the presence of a swelling had been noted. The presence of a bony nodule in the region of the epicondyle

31. Petrignani, R.: Rev. d'orthop. 18:105, 1931.

was the chief sign; sometimes it was tender and at others not. Patients who had been injured when at work often complained of more serious functional disturbances, but it was necessary to be on one's guard in accepting these. As far as the diagnosis was concerned, it depended chiefly on the roentgen examination.

The evolution of the bony nodule was variable; occasionally it completely disappeared in the course of time; more often it enlarged to a certain degree, then reached a degree of stability where it no longer changed and was relatively inert, and very rarely it might evolve into a large mass and cause considerable disturbance. Only rarely was surgical removal necessary, and this was indicated only when the ossification had reached a state of maturity and was voluminous in size, bothersome and painful.

Osteochondritis Dissecans.—Böhler³² denied that osteochondritis dissecans was of traumatic origin. In a large experience with traumatic bony injuries he had observed many intra-articular fractures with separation of bone fragments of various sizes, but had never seen any that resulted in an appearance similar to that seen in osteochondritis dissecans. He was inclined to feel that this lesion had its origin in endocrine dysfunction, perhaps stimulated or resulting from environmental conditions.

Roentgen Evidence of Lead Poisoning.—Park and his co-workers³³ reported four cases of chronic lead poisoning in children with shadows at the ends of the growing bones similar to those described after continued administration of phosphorus. The authors believed that these shadows occurred only when lead had been taken sufficiently long and in sufficiently large dosage. The changes were best observed in the more rapidly growing parts of the skeleton, and were most marked in very young children. Two of the cases came to autopsy. In the long bones the trabeculae were found to be far more numerous than in normal bones at the zone of provisional calcification. The shadows were due either to this modification of the trabeculae or to actual deposition of lead here, or both.

[ED. NOTE.—Although the orthopedic surgeon is not likely to be called on to diagnose or treat lead poisoning in children, it is important for him to know the possible causes of abnormal appearance of the bone as revealed by roentgenograms, and the work of Park and his co-workers ought to interest him from this standpoint.]

32. Böhler, L.: München. med. Wchnschr. 77:109, 1930.

33. Park, E. A.; Jackson, D., and Kajdi, L.: Shadows Produced by Lead in X-Ray Pictures of Growing Skeleton, Am. J. Dis. Child. 41:485 (March) 1931.

SURGERY OF BONES, JOINTS AND TENDONS

Treatment for Paralytic Deformities by the American and German Schools of Orthopedic Surgery.—Reviewing the various orthopedic procedures employed in the treatment for paralytic deformities by the American and German schools, Lange³⁴ pointed out that there was no essential difference of opinion in respect to paralyses of the knee and arm. In both countries paralyses of the knee were treated either by tendon transplantation or braces, or both, rather than by arthrodeses. In the case of the arm, arthrodesing operations were done at the shoulder or wrist only when there were no muscles sufficiently strong to be worth transplanting. Paralytic scoliosis was usually treated in Germany by supporting braces and exercises, while the operation of spinal fusion was often resorted to in America. In hip paralyses the German orthopedic surgeons preferred muscle transplantation, while in the United States such operations were not frequently performed. Bone and joint operations were for the most part not done before the fourteenth year in German clinics. Before this age deformities were prevented or corrected by exercises, manipulations and tendon transplantations. After the fifteenth year, both the American and German schools were in accord that paralytic deformities of the feet should be corrected by operations chiefly attacking and fusing the subastragalar joint while preserving as much motion as possible at the ankle joint.

The Arthroscope.—A preliminary report of a method of direct visual examination of a joint with the opportunity for the removal of specimens of tissue by means of an arthroscope was made by Mayer and Finkelstein.³⁵ Special instruments had been devised to be employed in conjunction with the arthroscope. Three case histories were reported in which the method had been used. The authors stated that though the value of the method was at the present time problematic, their experience had encouraged them in the belief that the instrument would enable more accurate diagnosis of joint lesions than any method previously devised.

[ED. NOTE.—The idea of arthroscopy is not new, and previous investigations along this line have been made by other authors. Mayer and Finkelstein seem to have refined the apparatus and the technic. The weakness of arthroscopy lies in the fact that it is itself an operation and may involve greater risk while yielding less information and less opportunity for treatment than an exploratory operation.]

34. Lange, F.: J. Bone & Joint Surg. **13**:479, 1931.

35. Mayer, L., and Finkelstein, H.: J. Bone & Joint Surg. **13**:583, 1931.

Lacerated Wounds Involving Tendons.—Böhler³⁶ warned the general practitioner against undertaking the difficult task of suturing injured tendons, and advised him to confine his attentions only to providing first aid care of the wound, and to send the patient as quickly as possible to a hospital where suitable facilities for thorough treatment were available. When immediate hospitalization was not possible because of distance or other causes, the best thing to do was to clean the wound and close it, but without suture of the injured tendon. Even in hospitals only smoothly severed tendons should be sutured primarily; other cases with lacerations of the tendons, extensive trauma of the soft tissues or injuries of the bones should be reserved for secondary suture. But even this ought not to be attempted when the structure damaged was the flexor tendon of the finger at the level of the proximal phalanx on account of the uniformly bad results obtained by any type of suture.

[ED. NOTE.—Even admitting that the results of suture of the flexor tendons of the fingers are uniformly bad, there are still enough exceptions to this rule to justify trial of the method in selected cases. The only other alternatives are late tendon transplantation, a procedure that is often unsuccessful, or amputation. A stiff finger is always a great handicap to an otherwise normally functioning hand.]

Arthrodesis of the Hip.—A method was described by Abbott and Fischer³⁷ for securing ankylosis of the hip in cases of tuberculous arthritis in which the head and neck of the femur had been completely destroyed and the acetabulum markedly eroded. The procedure had been carried out in several stages; first, the correction of deformity; second, arthrodesis of the hip by denudation of the bony surfaces with fixation of the hip in wide abduction almost at a right angle to the axis of the body, and third, reduction of the widely abducted position of the hip after ankylosis had been obtained by subtrochanteric osteotomy.

The authors reported the cases of eleven patients, all with advanced destruction of the hip, in whom the method had been employed and in whom highly satisfactory results had been obtained except in the case of two patients who had discharging sinuses. In one of the latter an incomplete ankylosis and a discharging sinus still remained at the end of eleven months, while in the other case clinical ankylosis with healed sinuses was present after fourteen months. All of the others were able to walk and sit in comfort without pain. In seven cases the average time before roentgen evidence of beginning ankylosis was obtained was four and one-half months. The average length of time

36. Böhler, L.: *Med. Welt* 4:1030, 1930.

37. Abbott, L. C., and Fischer, F. J.: *Surg., Gynec. & Obst.* 52:863, 1931.

elapsing between the arthrodesis and the correction of wide abduction by osteotomy was five and nine-tenth months.

[ED. NOTE.—No definite conclusion in respect to the value of the procedure described by Abbott and Fischer can be drawn before more extensive trial has been made of it by other surgeons. It is to be noted, however, that it is intended to be used only in that group of cases in which there has been extensive bony destruction or dislocation, the type that is most difficult to fuse by ordinary methods. We feel that the stability of the hip together with the close approximation of the bony surfaces obtained by the position of extreme abduction ought to conduce toward obtaining ankylosis. If this can be obtained with certainty in a high percentage of cases the disadvantage of a subsequent osteotomy ought to be regarded in comparison as of only slight importance.]

Transplantation of the Biceps Femoris Muscle for Quadriceps Paralysis.—Crego and Fischer³⁸ studied the end-results in sixty-one patients in whom the biceps femoris muscle had been transplanted for paralysis of the quadriceps femoris muscle. The ages at which the operation had been done ranged from 5 to 22 years. Of sixty patients with satisfactory results, only three had power in the quadriceps at the time of operation. In six patients there had occurred a varying degree of return of power in the quadriceps. One case was a failure due to lack of cooperation in the after-treatment. The authors stated that the operation was contraindicated in the presence of deformity of the knee or hip, in the absence of sufficient posterior support of the knee and where there was no possibility of discarding mechanical support. In the operation itself it was necessary to prepare an adequate patellar bed for the transplanted tendon; also to free the biceps femoris upward sufficiently to secure the maximum oblique pull, and also to suture the biceps tendon firmly to its new insertion under tension with the knee fully extended. To insure a good functional result exercises and massage had to be begun in the third or fourth week, and mechanical support for the knee ought to be worn for a year. Exercise treatment of the knee ought to be continued from twelve to eighteen months. The common complication was genu recurvatum. It was best treated by prolonged mechanical support of the knee, holding it in slight flexion.

FRACTURES

The Breaking Strength of Healing Fractures.—The breaking strength of a healing fracture was studied by Howes and Lindsay³⁹ in the fibula of the rat. A standardized type of experimental fracture was

38. Crego, C. H., and Fischer, F. J.: *J. Bone & Joint Surg.* **13**:515, 1931.

39. Howes, E. L., and Lindsay, M. G.: *J. Bone & Joint Surg.* **13**:491, 1931.

produced by cutting the fibula with a scissors in each of 250 rats. The animals were killed in groups of five at three day intervals, and the specimens recovered. Each of the specimens was subjected to tests in a machine which accurately measured the resistance of the newly formed callus to tensile strain.

The authors found no resistance at the fracture site before the sixth day, but that after this the strength of the callus increased rapidly to the twenty-first day. It then diminished to the thirtieth day, when it rose again to a permanently high level. The authors felt these findings agreed with the clinical and histologic observations on healing fractures. The first period up to the sixth day corresponded to the preliminary process of fibrosis. The second period up to the twenty-first day corresponded to the period of increasing size of the callus and deposition of calcium in the evolutionary tissue. The loss of strength after the twenty-first day was in accord with the histologic period of resorption preceding reorganization. The returning strength from the thirtieth to forty-fifth day coincided with the reorganization of the callus into normal bony structure.

Splint Grafts in the Treatment for Ununited Fractures.—According to Phemister,⁴⁰ ununited fractures in which there was little or no displacement or angulation of the fragments might be treated satisfactorily by the simple application to the ends of the fragments of whole thickness splint grafts or in some cases of osteoperiosteal grafts bridging the fracture line and held in position by suture of the enveloping soft parts. He considered intramedullary grafts as unsuitable in the treatment for ununited fractures, but thought that Høglund's sliding graft might be used in fresh fractures and in cases of delayed union in which marked displacement of the fragments was an indication for operation. A broad inlay graft turned on edge and made to fill both the medullary cavity and the slot cut in the cortex afforded a suitable method of treatment for cases of nonunion of the large bones.

Fracture of the Clavicle Treated by Suspension and Traction.—From observation of sixty patients with fracture of the clavicle, de Brun⁴¹ felt that the treatment of choice which gave the most perfect healing in the shortest time was the suspension and traction method. The shortening of the clavicle with shoulder deformity and faulty posture was negligible, and practically no after-treatment was required because early motion was practiced in all cases. The subsequent strap-

40. Phemister, D. B.: Surg., Gynec. & Obst. **52**:376, 1931.

41. de Brun, H. C. W. S.: Fracture of Clavicle Treated by Suspension and Traction, Followed by Strapping, J. A. M. A. **96**:1766 (May 23) 1931.

ping was utilized merely to remind the patient that he had had an injury to the shoulder girdle, and that some caution was still necessary.

[ED. NOTE.—The editors disagree with the author's views on the treatment for fracture of the clavicle, and believe that save in exceptional cases just as good or better results can be obtained from ambulatory treatment as from recumbent treatment in traction and suspension. Nor do we believe that it is necessary to immobilize the shoulder or arm for more than a brief period. Many types of apparatus have been described that maintain reduction while allowing use of the arm. Not only our own experience, but that of students of fractures in general, warrants the statement that the common type of fracture of the clavicle is a singularly benign lesion which in a high percentage of cases recovers with complete function and slight, if any, anatomic deformity and in an unusually short period of time.]

Compression Fractures of the Spine.—Watson-Jones⁴² recorded seven cases of compression fracture of the spine treated by manipulative reduction. One patient died four weeks later of uremia. In the other six, treated within a few days of the injury, successful reduction was obtained. To accomplish reduction the author suspended the body of the patient face downward between two tables, the proximal portion of the thighs resting on the edge of one table and the shoulders supported by the arms on the edge of the second table, which was on a higher plane than the first table. No anesthetic was given, and immediately the patient was in position a plaster of paris jacket was applied. The patient was permitted to walk at the end of ten days, and wore the plaster for four months. Of the six patients, four had resumed their normal occupations, one was still under treatment and the other had recovered from his spinal column injury, but was invalided on account of bilateral fracture of the tarsus.

Kümmell's Disease.—From personal observations and roentgen studies, O'Brien⁴³ concluded that Kümmell's disease was simply an unrecognized fracture of the spine. He advised reexamination of injured spines at a later period even when the original roentgenograms had been negative, since in certain instances a second set of films revealed a fracture with characteristic change in the osseous structure.

Traumatic Separation of the Symphysis Pubis.—Sever⁴⁴ reported that he had followed three patients with fracture of the pelvis and wide separation of the symphysis pubis. Complete functional recovery

42. Watson-Jones, R.: Brit. M. J. **1**:300, 1931.

43. O'Brien, F. W.: New England J. Med. **204**:641, 1931.

44. Sever, J. W.: New England J. Med. **204**:355, 1931.

resulted in spite of failure to approximate the two parts of the pubis and persistent wide displacement. The only treatment employed in addition to rest was a tight swathe about the pelvis. From this experience the author concluded that operation to secure alinement of the pubis was rarely necessary.

Osteosynthesis in Fractures of the Hip.—Henry⁴⁵ reported the results of an investigation of proximal osteosynthesis in experimentally produced fractures of the neck of the femur in dogs after the manner of Hey Groves. The head of the femur was removed from the acetabulum, placed in apposition with the neck and fixed with a nail or screw introduced through the proximal articular surface. The hip was then replaced in the socket and the wound closed. A nail was used in three animals, but failed to hold. A rustless steel screw was then used with coarse, double pitched thread, and a slot at each end. The spongiosa was found dense enough to hold the screw only near the proximal side of the femoral head and in the trochanter or cortex of the shaft. No immobilization was used. Seven of the dogs bore weight on the hip a few days after operation. Firm bony union was demonstrated by roentgenograms forty-nine days after operation. In the earliest specimen removed ninety-two days after operation there were normal bony trabeculae and the line of osteotomy could not be seen. The cartilage over the femoral head was normal. The author felt that healing might be expected in intracapsular fractures of the hip where there were early and accurate contact of the fractured surfaces and early functional stimulation of the circulation. These experiments showed that the capital fragment devoid of all soft parts and of vascular supply united and revived under proper physiologic conditions.

Fracture of the Tuberosities of the Tibia.—The results of a study of fifty fractures of similar type was reported by Swett, McPherson and Pike.⁴⁶ Most of these injuries resulted from automobile accidents. The authors divided the fractures of the upper end of the tibia into five groups: Group I consisted of fractures of both tuberosities; there were three cases. They were treated by manipulation; open reduction was resorted to only when good alinement could not be secured by other means. Group II was composed of fractures of the external tuberosity. These were the most common type and numbered 29. Treatment was by manipulation. Group III included fractures of the internal tuberosity, of which there were two cases. Here treatment was by manipulation with overcorrection in plaster. Group IV was composed of fractures of the tibial spine. There were ten of these cases. Treatment was

45. Henry, M. O.: J. Bone & Joint Surg. **13**:530, 1931.

46. Swett, P. B.; McPherson, S. H., and Pike, M. M.: New England J. Med. **204**:749, 1931.

by manipulation under anesthesia to secure full extension of the knee. If extension could not be obtained, either removal or suturing of the tibial spine was resorted to. Group V consisted of V-shaped fractures, of which there were 6 cases. All but one were satisfactorily reduced by manipulation. Good functional results were observed in almost all of the cases followed.

Kirschner's Wire in the Treatment for Fractures of the Lower Extremity.—Boppe⁴⁷ stated that in his opinion Kirschner's wire for securing skeletal traction in the treatment for fractures represented an important advance. He had employed the method in a number of patients with fractures, and had been impressed with the results. In fourteen patients with fractures of the lower end of the femur, the insertion of the wire had been transcondylar in twelve and through the tibial tuberosities in two. In fourteen fractures of the bones of the lower leg, he had always inserted the wire through the os calcis. The traction force used had varied from 30 pounds for the leg to from 40 to 45 pounds for the femur. The wire had been left in place until the beginning of callus formation. Active mobilization of the foot was begun in fractures of the leg after ten days, and of the knee in fractures of the femur between the twentieth and twenty-fifth days. The wire was removed after from twenty-five to forty-five days.

In the author's twenty-eight cases there were four instances in which the wire had been broken, and in one patient in whom the wire had been inserted too close to the anterior cortex of the tibia this had given way on the twenty-fifth day, but the fracture had already consolidated. Aside from the latter case, the wire had never cut through the bone, and there had been no infections. Of twenty-two fractures studied, consolidation had been obtained in a period of from forty to forty-five days for the leg and from fifty to sixty days for the femur. Anatomic reduction had been obtained in ten cases, and in eleven it had been approximative with conservation of the normal axis without angulation or with shortening of less than 1 cm.

[ED. NOTE.—We share Boppe's high opinion of the efficacy and advantages of Kirschner's wire as a means of obtaining skeletal traction in the treatment for fractures and in other conditions.]

Skeletal Fixation in Difficult Fractures of the Shafts of Long Bones.—Pitkin and Blackfield⁴⁸ described a procedure of treatment for difficult fractures of the long bones, and stated that they had employed it with success in twelve cases of compound fracture of both bones of the leg.

47. Boppe: Bull. et mém. Soc. nat. de chir. **57**:10, 1931.

48. Pitkin, H. C., and Blackfield, H. M.: J. Bone & Joint Surg. **13**:589, 1931.

Four pins were introduced in the upper and lower ends of the tibia, two above and two below the level of fracture. The ends of the pins were clamped by adjustable turnbuckles. A débridement was then performed, and after the wound had been cleaned, the fracture was exposed and reduced. The apparatus was then adjusted so as to maintain proper alinement and locked. The wound was closed and a plaster casing applied, incorporating the apparatus in it but not including the foot or knee. The patient was allowed up in from three to seven days, and weight-bearing in the apparatus with the aid of crutches permitted in from seven to twenty-one days.

[ED. NOTE.—We believe the method of skeletal fixation described may prove useful in certain difficult fractures. We consider it dangerous and unnecessary, however, to permit weight-bearing at the end of seven to twenty-one days regardless of how strong the method of fixation is.]

Isolated Fractures of the Tibia with Luxation of the Fibula.—Lambotte⁴⁹ called attention to fractures of the tibia accompanied by dislocation of the fibula, and said that they were probably less rare than ordinarily thought, but were commonly unrecognized. In order to be sure of diagnosing them it was necessary to make a roentgen examination of the entire segment of the limb. There were two types:

1. Isolated fracture of the tibia with dislocation of the upper end of the fibula, the equivalent in the lower leg of Monteggia's fracture of the forearm in the upper extremity. This injury was usually accompanied by a paralysis of the external popliteal nerve.

2. Isolated fracture of the tibia with dislocation of the lower end of the fibula.

Lambotte had treated patients with examples of each of these varieties of fractures. Although about fifteen instances of the first variety had been reported, the author's case seemed to have been the first of the second variety published. Both patients required open reduction.

RESEARCH

Influence of Urinary Tract Epithelium on the Formation of Bone.—Huggins⁵⁰ transplanted portions of the epithelial lining of the kidney pelvis, ureter and bladder of dogs and rabbits to various parts of the body, particularly the rectus sheath, and to synovial cavities, and found that bone associated with cyst formation was produced. The cystic

49. Lambotte, A.: Bull. et mém. Soc. nat. de chir. **57**:28, 1931.

50. Huggins, C. B.: Formation of Bone Under Influence of Epithelium of Urinary Tract, Arch. Surg. **22**:377 (March) 1931.

fluid contained a large amount of calcium and phosphorus. Bone seemed to be produced under the direct influence of the epithelial cells.

Bone was also found to form in a fascial transplant to the bladder from which the urine had been diverted, when the fascia was in close contact with the bladder epithelium.

The epithelium of the gallbladder, stomach, jejunum and prostate, when transplanted to fascia, did not lead to bone production.

Roentgen Irradiation of Bones.—In order to answer the question of whether the healing of fractures was delayed by the frequent exposures to the roentgen rays necessitated by modern methods of treatment, Schneller⁵¹ made an investigation of the actual dosage and time of exposure in a number of patients. With about ten different exposures he estimated the maximum dosage as about 15 per cent of a skin erythema dose. He concluded that this amount of exposure could not have any effect on the formation of callus.

Shouse and his co-workers⁵² exposed all of the bones of dogs to roentgen radiation, the abdominal viscera being protected by lead screens. The dosage was about three times the human epilation dose. The dogs remained in apparently normal health until eight days later, when they developed an intoxication and died within twenty-four hours. Autopsy showed extensive capillary hemorrhage of all the organs. The substance of the spleen and of the lymph nodes was reduced, and the germinal centers alone remained. The bone marrow showed only connective tissue, fat, blood vessel endothelium, phagocytic cells and occasional normoblasts. The blood showed a marked leukopenia and deficiency in platelets.

[ED. NOTE.—These two articles supplement each other; one represents a warning of what may happen with excessive roentgen radiation of the bones, while the other strikes a note of reassurance by showing that we rarely approach the danger mark in our routine examinations. That there is a danger point, however, needs to be appreciated by all.]

51. Schneller, P.: Zentralbl. f. Chir. **57**:1414, 1930.

52. Shouse, S. S.; Warren, S. L., and Whipple, G. H.: J. Exper. Med. **53**:421, 1931.

IRRADIATION OF MAMMARY CANCER, WITH SPECIAL REFERENCE TO MEASURED TISSUE DOSAGE *

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Carcinoma situated in the breast has certain physical advantages for treatment by irradiation. The mammary gland is superficial enough so that any tumor in its depth may receive a considerable percentage of the energy from external sources of radiation. The accessibility of the breast permits a reasonably correct measurement of the tumor, an accurate estimation of the dosage and the proper implantation of radioactive foci. The reactionary phenomena following irradiation of the breast are of little moment and are seldom complicated by sloughing and infection, which are frequently present in tumors of the respiratory, genito-urinary and alimentary canals. The loss of mammary function is relatively unimportant to patients with carcinoma of the breast, since their average age is slightly over 50 years. Irradiation of mammary cancer does not contraindicate subsequent mastectomy; therefore the opportunity is afforded to apply various methods of irradiation, to amputate the breast, to study critically the histologic changes produced, and in certain cases to employ irradiation in proper dosage as the sole method of treatment.

Opposed to these advantages are certain undeniable handicaps to successful irradiation in cancer of the breast. The majority of mammary cancers are relatively radioresistant. The thick fat envelop of the breast is an extremely poor reactive tissue bed, which contributes little in the way of productive inflammation and fibrosis toward the destruction of carcinoma by irradiation. The delicate and moist skin of the axilla and sulcus of the breast will not tolerate much external irradiation. Many breast cancers metastasize widely before any treatment has been

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instituted; in such an event it is just as important (although more difficult) to destroy the metastatic carcinoma as it is the primary lesion.

We shall trace the evolution of methods of radiation for mammary cancer at the Memorial Hospital through the periods devoted to external irradiation only, the interstitial use of glass-filtered radon seeds, the employment of puncture by platinum-filtered radium needles, to the present mode of external irradiation followed by the interstitial deposition of gold radon seeds. Since July, 1929, 130 patients with primary operable and inoperable carcinomas of the breast have been treated by measured tissue doses of irradiation, expressed in terms of skin erythema units. The patients were divided into various groups; some were treated by roentgen rays only, others by external irradiation with the 4 Gm. radium element pack, others by interstitial irradiation alone, and still others by various combinations of external and interstitial irradiation. In the primary operable cases, most of the breasts were removed, with the axillary contents, at variable intervals after the completion of treatment, and multiple and whole sections of the breast were subjected to careful microscopic study. This material afforded opportunities to judge the radiosensitivity of carcinomas of the breast in terms of biologic units of measurement, and finally to study the tissue changes produced by the different methods of irradiation.

Until recently, trial of the curative power of roentgen rays and radium had been limited largely to recurrent and primary inoperable carcinomas of the breast, which accounts to some extent for the slow progress in the methods of radiation therapy for mammary cancer. Although for one reason or another, in the past a considerable number of patients with primary operable carcinoma had been treated by irradiation alone, a carefully measured dosage had not been made, and the significance of histologic changes could not be evaluated. This information was obtained in the present study. Therefore we may generalize by saying that there is no phase or variety of this disease, operable, inoperable, recurrent or prophylactic, in which one may not make use of irradiation on a basis of accurate knowledge of treatment factors.

A. PRIMARY OPERABLE CARCINOMA OF THE BREAST

It is generally recognized that in the beginning cancer of the breast is a local disease, but that it remains localized for a comparatively short period. For prognosis, it is insufficient to group primary operable mammary cancers together without statements relative to the age of the patient, the presence of lactation, the rate of growth of the tumor, the size of the primary lesion and the presence or absence of homolateral operable metastases to the axillary lymph nodes. Lee formulated a clinical index of malignancy, based on these factors, which we shall use throughout our tables in lieu of more complete clinical data. Numerical

values are assigned to these various factors; the summation of these figures serves to divide the primary operable carcinomas of the breast into three arbitrary groups: (a) slightly malignant (relatively benign), (b) moderately malignant and (c) highly malignant.

The clinical diagnosis of carcinoma of the breast is seldom wrong, yet when a new nonsurgical method of treatment is under investigation, it is essential, for statistical purposes at least, to confirm the diagnosis

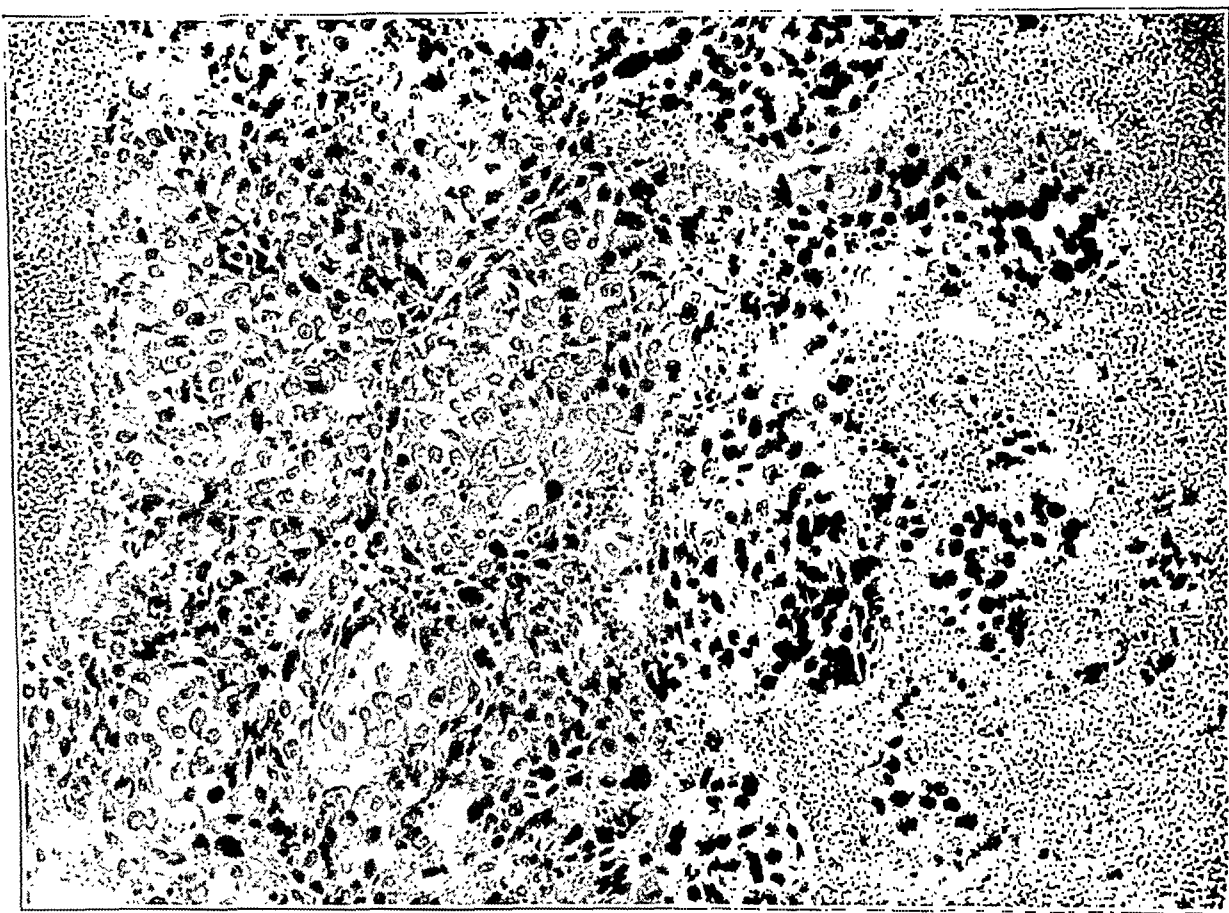


Fig. 1.—Section of a specimen of mammary cancer taken at biopsy by aspiration; method of Martin and Ellis of the Memorial Hospital.

by microscopic examination. In the cases in which subsequent mastectomies are contemplated, preliminary biopsies are unnecessary. When irradiation is the only treatment planned, the biopsy is obtained after external irradiation has been given and before interstitial irradiation has begun. Simple and safe methods of biopsy in use at the Memorial Hospital are the aspiration of these tumors through long, 18 gage needles, such as those perfected by Martin and Ellis, or punch removals of tiny portions of the carcinoma, followed by electrocoagulation of the needle track, as devised by W. J. Hoffman.

METHODS OF IRRADIATION AND SURGICAL INTERVENTION

In the management of primary operable carcinoma of the breast by irradiation and surgical intervention, there are at least seven possible methods.

Surgical Intervention Alone.—The type of radical mastectomy performed at the Memorial Hospital is a modification of the Willy Meyer-Halstead technic. A long, oblique, elliptical incision, encompassing the skin $2\frac{1}{2}$ inches (6.3 cm.) beyond the palpable margins of the tumor, is made from the junction of the pectoral fold with the arm to a point 2 inches (5 cm.) below the costal margin. Both pectoral muscles are removed, and a careful, wide dissection of the fat and fascia underlying the flaps of skin from the midsternal line to the latissimus dorsi is made. As far as is practicable, the dissection of the axilla is carried out from the apex, above and without, downward and inward, along the axillary vein; en masse removal is accomplished of the axillary contents, pectoral muscles, fascia, mammary gland and skin, the dissection ending below with a removal of fascia covering the rectus muscle. Few instances of local recurrence follow this complete operation. Following radical mastectomy, the percentage of survivals for five years without evidence of cancer is practically the same (35 per cent) in the leading surgical clinics of America and Europe. Improvements in operative technic do not promise decided betterment in the end-results. Surgical intervention alone cannot cope satisfactorily with the problem of mammary cancer.

External Irradiation Alone.—Roentgen rays or radium applied at a distance from the breast are only adjuvant measures, preliminary to the more radical procedures of interstitial irradiation or surgical intervention for the primary operable carcinomas. The amount of radiant energy reaching the depths of these tumors of the breast has always been insufficient to produce a lethal effect. As will be seen later, the physical measurement of the dosage delivered by these methods reveals why external irradiation alone can induce only growth restraint without sterilization of the carcinomas (table 7, patients L. R. and E. B.).

Interstitial Irradiation Alone.—The proper intratumoral espacement of radioactive foci in sufficient dosage may destroy the carcinoma, but the method of introducing the radium by puncture is theoretically fraught with the danger of disseminating the carcinoma cells. Furthermore, a slight error in the distribution of the radium in the tumor conceivably might permit certain of the carcinoma cells to survive.

External Plus Interstitial Irradiation.—When these two methods are employed consecutively, the external always precedes the interstitial irradiation. The menace of dissemination of the disease by the interstitial method is presumably lessened by preliminary external irradiation. This is the present procedure of choice for primary inoperable carcinomas of the breast, and when perfected may supplant surgical intervention as the ideal treatment in the primary operable group. By this method, the cosmetic and functional end-results in the breast and axilla are superior to those following surgical intervention. Hitherto, the only primary operable carcinomas of the breast purposely subjected to this treatment have been those that occurred in patients who had intercurrent diseases, such as diabetes, cardiac ailments and tuberculosis of so serious a nature as to contraindicate operative removal. Occasionally, the patient has absolutely refused to sacrifice her breast by amputation, in which circumstance the surgeon has elected the combination of external and interstitial irradiation as the only alternative. Sufficient time has not elapsed or experience accumulated to encourage the routine adoption

of this treatment, but because of our histologic studies following the proper application of this treatment, we are optimistic concerning its possibilities.

Interstitial Irradiation Plus Surgical Intervention.—With the proper dosage and the correct interval before mastectomy, the combination of interstitial irradiation plus operation affords a certain surety of destruction of the primary tumor (table 8). We have never observed any ill effects attributable to this method of treatment, although the theoretic dangers of the dissemination of cancer obtain in the absence of preliminary external irradiation.

External Irradiation Plus Surgical Intervention.—This method has been the usual treatment for primary operable mammary cancer during the last few years at the Memorial Hospital. The percentage of survivals for five year periods, without evidence of cancer is only about 5 per cent better than that by surgical intervention alone. Nevertheless, that preoperative external irradiation is of value is proved by the occasional marked regression in tumors so treated, by the histologic changes produced and by the better clinical end-results.

External and Interstitial Irradiation Plus Surgical Intervention.—We are treating patients with primary operable mammary cancer at present by external irradiation, then by interstitial irradiation followed by radical amputation six weeks or more later. The patients treated by measured tissue doses and by radical surgical intervention have not received postoperative roentgen treatments, as it was decided that the addition of such a procedure might invalidate the end-results of these clinical studies.

PREOPERATIVE EXTERNAL IRRADIATION

An efficient devitalizing dose of irradiation cannot be delivered by external irradiation alone, except in the case of certain unusual anaplastic cancers of the breast. The basis for the use of preoperative external irradiation depends partly on clinical experience and partly on histologic evidence. We have had ample demonstration at the Memorial Hospital that many cases of mammary cancer show a partial regression within from a few days to a few weeks after external irradiation, and that the occasional radiosensitive carcinoma may disappear. This diminution in size is the rule rather than the exception. Tumors become better defined, and in some of our inoperable cases in which fixation to deeper parts had formerly been present, definite mobility has been obtained. In general, the more highly malignant the tumor the greater the radiosensitivity and the more extensive are its clinical evidences of regression. In this manner, irradiation may serve as a therapeutic test of the malignancy of a carcinoma. One does not obtain this regression with such radioresistant tumors as the scirrhous and diffuse duct carcinomas of the breast. Our clinical experiences strongly favor the use of external irradiation prior to interstitial irradiation and operation in the attempt to convert, temporarily at least, a growing tumor into a regressive one.

Until 1920, the only roentgen-ray machines in use at the Memorial Hospital were those of the so-called low voltage type. The whole breast and adjacent regions were divided into four or six areas, each area being treated on successive

or alternate days, until all had been irradiated. In some instances, this type of treatment was given for months, with little or no intermission between cycles. The set-up for delivering the dose was as follows: a peak voltage varying between 120 and 155 kv., 5 ma. of current, from 2 to 4 mm. of aluminum filter, a focal distance of from 8 to $8\frac{3}{4}$ inches (around 21 cm.) and a treatment time of from three to six minutes. Later the time was lengthened to seven or eight minutes, the target-skin distance increased to 9 or 10 inches (around 23 cm.), but the number of aluminum filters was unchanged. Then, in 1921, the set-up included a peak voltage of 140 kv., 4 ma. of current, a filter of 4 mm. of aluminum, a target-skin distance of 12 inches (30.48 cm.), an exposure of fifteen minutes and an average portal of approximately 300 sq. cm. In 1922, with the same peak voltage of 140 kv., 4 ma. of current, 5 mm. of aluminum filter and a



Fig. 2.—The 4 Gm. radium element pack at the Memorial Hospital.

portal of entry of the same size were used; the target-skin distance was increased to 15 inches (37.54 cm.) and the time to twenty-five minutes. This set-up is still in use, especially for postoperative roentgen treatments over the lower portions of the anterior and lateral area of the chest.

All preoperative roentgen treatments are now given by the high voltage machines with the following factors, 200 kv., 30 ma., 50 cm. target-skin distance, and a filter of 0.5 mm. of copper and 2.5 mm. of aluminum.

The early "pack" for external radium therapy was constructed with a radiating area of 70 sq. cm., and a filter of 0.5 mm. of silver and 1 mm. of brass, which is the filtration equivalent of 2 mm. of brass. The radon pack carried an amount of emanation varying from 1,200 to 2,500 millicuries, and was placed at a distance of 6 cm. from the skin for an average dosage of 12,000 millicurie hours. This applicator has been largely supplanted by the present radium element pack, which contains 4 Gm. of radium. The radium-skin distance is 6 cm. The

filter is 0.3 mm. of platinum and 1.5 mm. of brass. For therapeutic purposes, the average dose is 16,000 milligram hours.

The usual cycle of irradiation of the breast, whether by high voltage roentgen rays or by radium element pack, consists of four exposures, namely, the first two over the breast proper and the last two over the axilla and supraclavicular regions. The first treatment over the breast proper is given in front and the second from the side, thus an additional portal of entry for cross-firing is used, thereby almost doubling the dose to the tumor and its environment. When the breast is small, the treatment by radium element pack can be given over only one area on the breast. It will be noted that the supraclavicular treatment augments the amount of irradiation to the apex of the axilla.

The radium element pack and the high voltage roentgen rays are different in their modes of application and in the results produced. The roentgen rays are more economical when a large number of patients are to be treated, because each dose may be given in from fifteen to sixty minutes. The radium element pack is a single applicator, and requires four hours to deliver a dose when placed at the usual distance of 6 cm. from the skin. This increased time of exposure is probably an advantage, as we shall explain when we consider the time factor.

With increasing filtration and higher voltage, there is a possibility that the effects of the roentgen rays will approximate the results produced by the gamma rays of radium. Under the present circumstances, however, these two closely related forms of radiant energy seem to produce different histologic changes in the carcinomas. In irradiated breasts, Ewing early observed a preponderance of injury and reaction in the connective tissue (mucinous swelling, fragmentation of collagen fibrils, interstitial hemorrhages and vascular changes) from roentgen rays and more direct injury to the tumor cells from radium. He stated that, "roentgen-rays have not yet reached the hardness upon which selective action appears to depend. There may be advantage in combining roentgen-rays and radium in the treatment of tumors."

Ewing's suggestion of the value of combining the two methods of external irradiation has been under trial for several years at the Memorial Hospital. Our experience in the treatment for mammary cancers has afforded clinical verification of the soundness of this theory. It is assumed that this apparent potentiation is due to the different effects of the gamma and roentgen rays on the carcinoma and its tissue bed. Apropos of this clinical observation, Quimby and Pack conducted a series of experiments which showed that the production of skin erythema by a half and half combination of gamma and roentgen rays required a total of 30 per cent more radiant energy than was required when either was employed alone. The result of this experiment cannot be applied to the treatment for cancer, since the cancer as well as the skin may tolerate the increased quantity of irradiation afforded in the delivery of an erythema dose by this combination. As Ewing has

inferred, however, these two agents do not seem to act by a summation of this effect, but chiefly by direct action on the tumor cells in the case of the gamma rays and indirectly by changes in the tissue bed in the case of roentgen rays.

The order of sequence of the radium and roentgen treatments is not an indifferent matter. When the combination is employed, the roentgen treatments should precede the irradiation by the radium element pack (table 12). The reactions in breast tissue following roentgen treatment appear later than do the changes produced in the tumor cells by the gamma rays. Another argument for this order of employment is based on the

TABLE 1.—*Percentage of Variations in Depth Dosage with Variation in the Size of the Field**

Depth, Cm.	Size of Field, Sq. Cm.					
	30	50	75	100	200	400
0	100	100	100	100	100	100
5	57	61	64	67	72	75
10	26	28	31	33	38	41

* The dose on the skin was constant at 100 per cent S. E. D.

TABLE 2.—*Depth Dose if the Skin Always Receives a Dose that Gives S. E. D. for a 100 sq. cm. Field*

Depth, Cm.	Size of Field, Sq. Cm.					
	30	50	75	100	200	400
0	90	94	97	100	104	106
5	51	57	62	67	75	80
10	23	26	32	33	40	44

experience gained in treating patients with malignant neoplasms in other locations, in which radium has proved successful after the roentgen rays have failed, and in which roentgen therapy has failed after radium treatments have been insufficient.

Particularly when the roentgen rays are employed, a large area of skin is exposed at each treatment. In the average case, this area measures 15 by 15 cm. The reasons for using such a large area are numerous. The first is that the entire diseased tissue and the surrounding normal tissues may be fully irradiated, for if one limits irradiation only to the palpable tumor, in some instances, an outlying nonpalpable cancer may escape control. Another reason for selecting large areas is that the larger the skin surface, the greater will be the depth dose because of the augmentation of this dose by the scattered radiation produced. In small breasts, this extra amount of scattered irradiation is negligible because of the small skin portals employed. The variations in dosage caused by this factor are shown in table 1.

The tray is a small external applicator for radium therapy; it contains radon at a distance of 3 cm. from the skin. The radiating surface measures 24 sq. cm. and the filter is 2 mm. of brass. The average dosage is 3,000 millicurie hours. This applicator is used chiefly for single, small, fixed recurrent nodules of carcinoma, although occasionally it is employed as a preoperative measure for small mammary cancers situated superficially at the periphery of the breast (table 11, patient, N. J.).

In light complexioned patients, especially in those with reddish hair and ruddy complexions, a skin erythema develops more readily than in brunettes. In treating the former, a dosage less than the average should be planned and given, or damage to the skin may follow. On the other hand, an erythema develops less readily in anemic and undernourished persons than in the average patient.

THE TIME FACTOR IN PREOPERATIVE IRRADIATION

Preoperative irradiation delays operation. Objection may be raised to such delay on the ground that it may permit extension of the disease, but it appears probable that carcinoma subjected to irradiation even by external methods alone is less likely to metastasize. Moreover, we believe that when a tumor and its drainage areas have been properly irradiated by roentgen rays or the radium element pack, neoplastic cells dislodged during the subsequent operation are less likely to remain viable, and thus the menace of recurrence is diminished. After interstitial irradiation, the interval of time before mastectomy is still greater, because of the persistent radium reaction. The radon deposited within the breast has an exponential rate of decay, less than 6 per cent remaining at the end of thirty days. The irradiation, therefore, by this interstitial method is continuous, but with diminishing intensity.

With regard to the factor of time, there are three principal methods for irradiating mammary cancer.

The Single Efficient Killing Dose.—This dose cannot be delivered by external irradiation, because the skin of the breast will not tolerate an exposure of a sufficient amount to deliver a sterilizing dose to the depths of the tumor. Interstitial irradiation is the only method known at present that furnishes sufficient intensity to destroy the average cancer of the breast.

The Prolonged Single Treatment by External Irradiation.—The principle of this method was established by Régaud at the Curie Institute of the University of Paris. It is generally accepted that in the course of its existence, a cell or a line of cells (cancer cells especially) pass through alternating phases of radiosensitivity and radioresistance. The cells are particularly radioresistant when they have been in a state of

repose or rest for a long time. They are most sensitive to the action of radium or roentgen rays when they are in a state of mitosis or indirect cell division (law of Bergonié and Tribondeau). A short treatment, therefore, would destroy only the cancer cells that are dividing at that time; it spares the others. As the mitotic cycle continues, the various resting cells divide and thereby come under the influence of continuous irradiation. In the treatment for mammary cancer at the Memorial Hospital we have not applied this form of irradiation. Part of the superiority of the radium element pack may be attributed to the fact that the time consumed in treatment is from four to twenty times as long as when the roentgen rays are used. The radon deposited in gold seeds within the tumor is constantly active for twenty-four hours daily, so the advantage of the interstitial method may be due to its continuous action as well as to the intensity of the irradiation. The time of administering a dose of irradiation may vary within wide limits without modifying the degree of tissue reaction or tumor response, providing the treatment does not consume a period equivalent to the life cycle of the normal or cancer cell. Comparative studies on the efficacy of different intensities of radiation in the treatment for cancer are of value only when the duration of exposure in the one experiment is greater than the life cycle of the cancer cell, and the duration of exposure in the other experiment (i. e., greater intensity) is less than the life cycle of the cancer cell.

Ewing considered the prolonged single exposure by external irradiation as the ideal, selective, nondestructive form of radiation therapy, designed to kill dividing cells and to induce gradual atrophy of the tumor cells, but he admitted that its chief indication is for palliation of advanced inoperable or recurrent cancers.

Fractionated Dosage.—This method should never be used in the treatment for operable carcinoma of the breast. The principle underlying its usage has been defined by Ewing as "the cumulative effect of successive doses delivered upon cells rendered vulnerable by the hyperemia and degeneration excited by previous doses." Fractionated dosage applies only to external sources of radiation; when interstitial irradiation is used, the entire amount of radon is introduced at one time. Fractionated dosage by roentgen rays or radium element pack is often suitable for advanced mammary cancers in which abortive fibrosis and growth restraint rather than a cure are expected. Among the many disadvantages of this method are the severe tissue reaction induced, the prolonged delay if subsequent mastectomy is contemplated, the impaired healing of the operative wound because of the fibrosis and impoverished blood supply, and the acquisition of increased radio-resistance by the carcinoma.

The entire radiation therapy should be given within three weeks. A prolongation of this period not only renders the radiation less effective,

but adds the probable complication of acquired radioresistance, which is as important a factor as the tissue dose. In order to appraise the method of irradiation, it is necessary that the time consumed be fairly constant. As a rule eight days are required for the average cycle of roentgen treatments for the breast; the same exposures by the radium pack are given within a ten day limit. External irradiation is preferably followed in a day or two by the introduction of the gold radon seeds into the breast and axilla. The radon thus deposited within the breast continues to irradiate the tumor but with diminishing intensity, so that most of the activity is spent during the ensuing fortnight. There is some question in our minds concerning the relative effectiveness of continuous irradiation by radon with an exponential diminution in intensity, as compared with radium element used interstitially, with a constantly equal intensity during an equivalent continuous period.

THE PHYSICAL PRINCIPLES UNDERLYING THE ESTIMATION OF TISSUE DOSAGE

Any intelligent discussion of the effect of radiation must be based on an estimate of the quantity actually producing the phenomenon. In the case of regression of a tumor mass, whether one considers the effect to be a direct one on the malignant cells or a more or less indirect one due to changes produced in the "tumor bed," it must be conceded that it is the amount of radiation actually delivered in that region that is significant. Moreover, it is evident that all points of an irradiated mass cannot receive the same amount of energy; this is particularly true when interstitial radiation is employed. If tumor regression depends on every point receiving at least a definite amount of energy, then it is necessary to know the quantity delivered at the point that received the minimum. It is evident that for external radiation, a knowledge of the amount leaving the source or falling on the skin is of little value, because the amount delivered at a point within the body varies enormously with the depth below the skin. For example, the notation "so many milliamperes-minutes" is the correct expression for the dose of emission, but at a target-skin distance of 50 cm. the tumor may be from 50 to 70 cm. from the source of the roentgen rays, and therefore the amount of radiation it receives may vary from 50 to 100 per cent of the skin dose.

In the case of interstitial radiation, a knowledge of the amount used is not sufficient. One must also know the size and shape of the mass, the distribution of the sources and the manner in which the effect varies with the distances from the sources.

It is customary to call the amount of radiation delivered at a given point in the tissue the "tissue dose" at that point. The tissue dose of a given volume of tumor is estimated according to the point within it

that receives the smallest quantity of energy. At the Memorial Hospital, our unit of quantity of radiation in terms of which all tissue doses are expressed is the threshold erythema dose. This is defined as the amount of radiation which, in 80 per cent of all cases after a single application, will produce a faint bronzing or reddening of the skin in about three weeks, and in the other 20 per cent will produce no visible effect. We grant that this unit is not entirely satisfactory, but we find it the best available at present. Full discussions of its use have been previously published. Although the quantitative basis is the best we have for tissue dosage, the response of the various mammary cancers to this same dosage is qualitative, and we have no absolute biologic unit to express this response. The threshold erythema doses for sources

TABLE 3.—*Depth Doses from External Sources of Irradiation*

Depth, Cm.	Roentgen Rays		Gamma Rays	
	200 kv., 0.5 Cu. Min., 2.5 Mm. Alumi- num Filter, 50 Cm. Target- Skin Distance	140 kv., 4 Mm. Alumi- num Filter, 30 Cm. Target-Skin Distance	Radium Element Pack: 0.3 Mm. Platinum, 1.5 Mm. Brass Filter, 50 Sq. Cm. Radiat- ing Surface, 6 Cm. Radium- Skin Distance	Radon Tray: 2 Mm. Brass Filter, 24 Sq. Cm. Radiat- ing Surface, 3 Cm. Radium- Skin Distance
0	100	100	100	100
1	99	91	75	62
3	85	66	51	27
5	67	48	35	13
7	52	36	25	8
10	33	22	16	4
12	25	15	12	
15	17	9	3	

of radium and roentgen rays in use at the hospital have been determined by skin tests on a large number of patients. By means of physical experiments, the percentage of the amount of radiation falling on the skin that arrives at any depth within the tissue has been determined. In treatment for cancer of the breast, the external sources used are roentgen rays of various qualities, the radium element pack and, to a less extent, the radon tray. Table 3 shows the percentage of surface radiation arriving at various depths for these sources.

From this table, if the amount of radiation falling on the skin at each portal is known in terms of the threshold erythema (S. E. D.¹), and if the depth of the tumor below each portal is also known, the tissue dose from external radiation can be determined at once. Figure 3 and figure 4 represent a transverse cross-section of a breast, showing the irradiation by two radium pack treatments (fig. 3) and two high voltage roentgen treatments (fig. 4). In each case one treatment is from the

1. Hereafter the threshold erythema dose will be expressed by the letters S. E. D. (skin erythema dose).

anterior and the other from the lateral direction. Only within a limited region can more than one erythema dose be delivered in this manner.

In interstitial radiation the problem is not so simple. The interstitial sources used at present at the Memorial Hospital are gold seeds

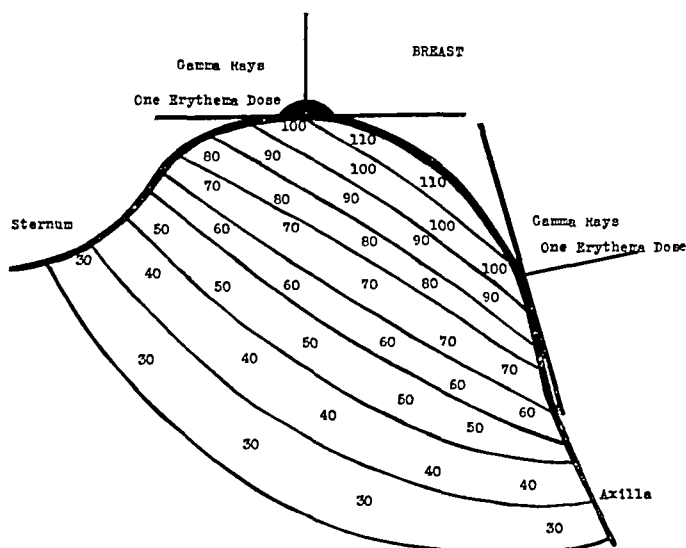


Fig. 3.—Transverse cross-section of a breast showing the depth of doses of irradiation by two radium pack treatments.

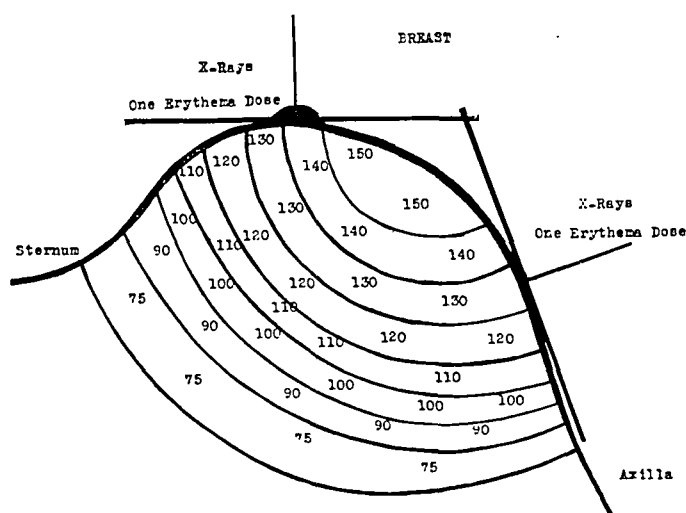


Fig. 4.—Transverse cross-section of a breast showing the depth of doses of irradiation by two high voltage roentgen treatments.

about 4 mm. long, 0.3 mm. in width and thickness and containing from 1 to 3 millicuries of radon. Experimental work previously published makes possible the determination of the percentage of a threshold erythema dose delivered at any distance from any gold seed. The values for a seed of 1 millicurie at different distances are shown in

table 4. For seeds of other strengths, the doses are in the ratio of the millicurie content.

It should be emphasized that the values up to 1.5 are based on much more complete experimental data than those for longer distances. Therefore, in using this table it should be remembered that the data for larger distances may be less accurate than those for shorter ones. With the aid of this table, if one had a chart of any tumor of the breast with the locations and strengths of the seeds that had been implanted, one could measure all their doses from any selected point and find the tissue doses at that point due to the individual seeds.

It is impracticable to do this in actual cases. In the report already referred to, the problem of estimating dosage in masses has been discussed at length, and only the conclusions will be repeated here. We

TABLE 4.—*Tissue Doses at Different Distances from a 1 Millicurie Gold Radon Seed*

Distance, Cm.	Tissue Dose, Percentage, Skin Erythema Dose	Distance, Cm.	Tissue Dose, Percentage, Skin Erythema Dose
0.5.....	475	1.8.....	40
0.6.....	350	2.0.....	35
0.7.....	230	2.5.....	25
0.8.....	175	3.0.....	20
0.9.....	140	3.5.....	15
1.0.....	115	4.0.....	12
1.2.....	70	4.5.....	10
1.4.....	55	5.0.....	8
1.6.....	45		

have assumed that it is necessary for every point within the region of the tumor to receive at least a certain minimum dose; and it is the tissue dose for the point receiving the minimum that should be calculated. In a mass in which seeds are uniformly implanted, this point will be on the periphery rather than somewhere inside. For every mass, it is most convenient to consider the sphere of tissue that will just contain it. Of course, in the case of very much elongated or irregular masses, this would include a great deal of normal tissue, and in such types several contiguous or overlapping spheres may be considered. If a definite quantity of radon is to be used in any given sphere, it makes practically no difference in the dose on the periphery whether the radon be concentrated at the center or distributed uniformly within the inner half of the sphere. Therefore, for purposes of approximation of dosage, we consider the radon that is concentrated at the center of the sphere that just contains the mass, and calculate for the minimum the dose at a point on the periphery. Thus a mass 2 by 2 by 3 cm. would be considered a 3 cm. sphere. One millicurie of radon at the center of this (1.5 cm. from the surface) would deliver 50 per cent of an erythema dose on the periphery (table 3). Ten millicuries would

deliver ten times as much, or 500 per cent—5 S. E. D. Therefore, if a mass of this size were treated with 10 millicuries, we should call its tissue dose 5 S. E. D. It is well to keep in mind the approximations used in arriving at this result. The same approximations enter into all the doses quoted in this paper. The fact that the doses are not highly accurate does not lessen the clinical value of the measurements.

For convenience in calculation, we have made a table of doses for different quantities of radon in spheres of different sizes. This is given in table 5. Across the top are indicated the sizes of the masses considered. The first column gives the number of erythema doses, and

TABLE 5.—*Millicuries in Gold Seed Required to Deliver Specified Doses to Masses of Various Diameters*

Skin Erythema Doses	Diameter of Mass, Cm.											
	1	1.5	2	2.5	3	3.5	4	4.5	5	6	7	8
	Number of M.C.											
1.....	0.2	0.5	0.8	1.5	2	2.4	2.9	3.4	4	5.4	7	9
2.....	0.4	1.0	1.6	3.0	4	4.8	5.8	6.9	8	11.0	14	18
3.....	0.6	1.5	2.4	4.5	6	7.2	8.7	10.0	12	16.0	21	27
4.....	0.8	2.0	3.2	6.0	8	9.6	12.0	14.0	16	22.0	28	36
5.....	1.0	2.5	4.0	7.5	10	12.0	14.0	17.0	20	27.0	35	45
6.....	1.2	3.0	4.8	9.0	12	14.0	17.0	20.0	24	32.0	42	54
7.....	1.4	3.5	5.6	10.0	14	17.0	20.0	24.0	28	38.0	49	63
8.....	1.6	4.0	6.4	12.0	16	19.0	23.0	27.0	32	43.0	56	72
9.....	1.8	4.5	7.2	14.0	18	22.0	26.0	31.0	36	49.0	63	81
10.....	2.0	5.0	8.0	15.0	20	24.0	29.0	34.0	40	54.0	70	90
11.....	2.2	5.5	8.8	17.0	22	26.0	32.0	37.0	44	59.0	77	99
12.....	2.4	6.0	9.6	18.0	24	29.0	35.0	41.0	48	65.0	84	108
13.....	2.6	6.5	10.0	20.0	26	31.0	38.0	44.0	52	70.0	91	117
14.....	2.8	7.0	12.0	21.0	28	34.0	41.0	48.0	56	76.0	98	126
15.....	3.0	7.5	13.0	23.0	30	36.0	44.0	51.0	60	81.0	105	135

the others the number of millicuries required to produce these in masses of the sizes considered. For instance, in the column for 3 cm. diameter, we see that 10 millicuries delivers five erythema doses.

It should be mentioned that the data for diameters up to 3 cm. are based directly on measurements of skin erythema doses. Greater distances are calculated from these values on a basis of extensive experimental work in the biophysical laboratory, therefore, they cannot be considered as accurate as the former. However, we have no hesitancy in using them in our calculations of dosage.

THE TECHNIC OF INTERSTITIAL IRRADIATION

Interstitial irradiation as now employed at the Memorial Hospital consists in the distribution of tiny, nonremovable, gold-filtered radon seeds within the substance of the tumor, in the tissues of the breast surrounding the tumor and in the corresponding axilla. In contrast to

the more radical surgical measures, there is no mortality consequent to the introduction of these gold radon seeds; patients with serious cardiac ailments, diabetes, pulmonary tuberculosis, etc., have been treated safely by this method. The possible menace of dissemination of the disease by the method of interstitial irradiation has been considered; we believe that preliminary external irradiation greatly lessens this menace. Thus far we have not observed any untoward results from this procedure, such as early metastases to the bones and the lungs.

Preparatory to inserting the gold radon seeds into the breast, the entire area is prepared carefully as for a major surgical operation. The

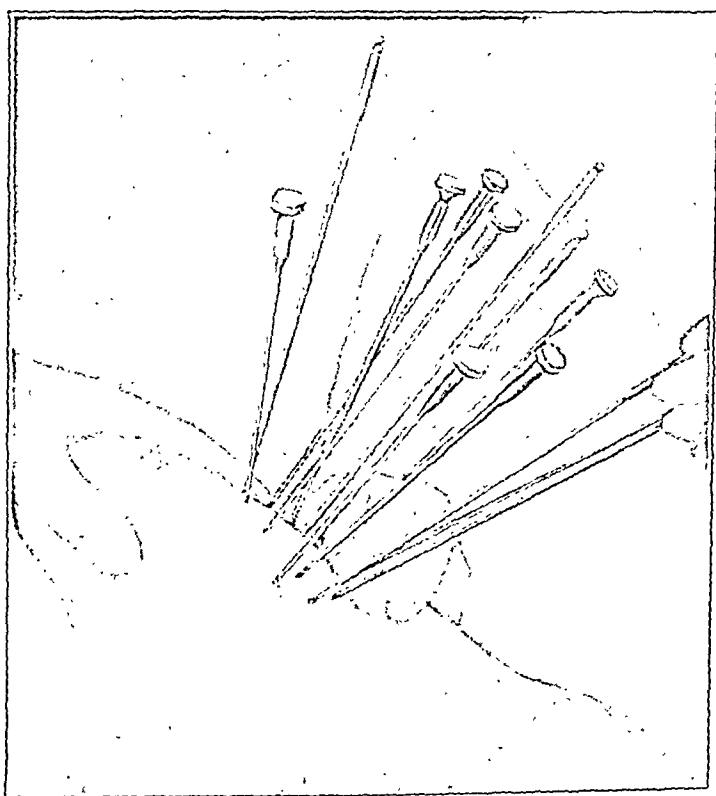


Fig. 5.—Technic of implantation of gold radon seeds in carcinoma of the left breast.

proper use of antisepsis and sterile drapery is essential in order to avoid infection of the cancer. In only one instance among our group of 130 cases did the complication of infection occur; the resultant abscess in the breast was a considerable handicap in the subsequent management of the case and greatly delayed convalescence.

If the tumor is large, nitrogen monoxide anesthesia is used for the very brief time required for the insertion of the seeds. In a few instances, the breast and axilla have been anesthetized by procaine hydrochloride in the outpatient department; this is sufficient when the tumor is small. One word of caution about local anesthesia should be given; if the skin is infiltrated or invaded by the carcinoma,

there exists a definite contraindication to the insertion of procaine hydrochloride solution, for fear of disseminating the disease. The majority of the patients leave the hospital within an hour or two after the insertion of the seeds and remain ambulatory during the entire course of the preoperative treatment.

Each gold radon seed is sterilized in alcohol and placed within a sterile long needle trocar carrying a minute metal plunger for the purpose of dislodging the seed into the depths of the tumor. These needles have sharpened points and are only 1.3 mm. in diameter, in order to cause the least possible trauma. Caution should be exercised that the tubes or seeds are not placed near the skin, otherwise

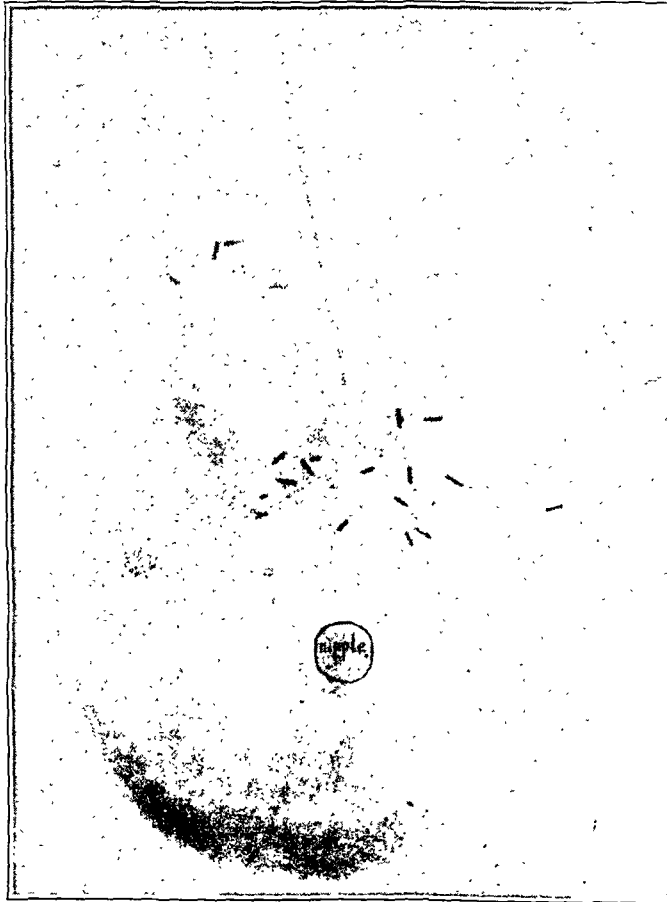


Fig. 6.—Roentgenogram of the right breast, showing the location of gold radon seeds in an irregular mammary cancer.

they may cause ulceration. Also one should be careful to avoid placing the seeds against a rib or costochondral junction, because of the possibility of injuring the periosteum or cartilage. If the tumor is spherical, the seeds are placed approximately one third of the distance to the center along the various radii, care being taken to place them at all levels.

The placement of gold seeds in tumors less than 4 cm. in diameter is fairly accurate, as the subsequent microscopic examinations reveal, but in the treatment of tumors from 6 to 8 cm. in diameter, unavoidable

errors in technic are constantly present to a variable degree, because it is not humanly possible to distribute tiny gold seeds accurately throughout a mass of these dimensions. As we have stated previously, it makes practically no difference in the dose on the periphery whether the radon is concentrated at the center or distributed uniformly within the inner half of the spherical tumor. Indeed in small spheres, such as single discrete axillary nodes, the entire estimated quantity of radon may be inserted in the center of such a node in a single gold seed focus. The use of a single focus of interstitial irradiation in the center of a mammary cancer, though physically correct, is practically unwise, as the central necrosis thereby induced by such a quantity of radon (i. e., from 30 to 90 millicuries) could not be as easily absorbed as if multiple weaker gold radon seeds were utilized.

THE PROPER TISSUE DOSAGE OF IRRADIATION

What are the advantages of measuring tissue doses of irradiation? The knowledge of the exact amount of radiant energy delivered to the tumor mass gives a rational basis for dosage and eliminates previous empiric methods. The routine estimation and recording of such tissue doses enables one to duplicate good results and to determine the sterilizing dose for various neoplasms. The knowledge of this tissue dose is important in the later microscopic study of the pathologic changes produced.

When external irradiation is employed, all other conditions remaining unchanged, the dose is equal to the product of two factors, namely, the intensity of the rays and the time of irradiation. Without modifying the product, one may vary either the intensity or the time, on the condition that a compensation of the variation of the one by an inverse variation of the other be made. Except for the theoretical advantages of continuous overinterrupted exposures, and the greater selective cancericidal effect of gamma rays over roentgen rays, we have assumed a quantitative equality for these rays and have added the dosage, whenever a combination of these methods was used.

To deliver an efficient dose into a mammary cancer, one must use interstitial irradiation. In the few unusual instances, wherein extremely radiosensitive carcinomas of the breast disappeared completely after external irradiation alone, we have not been content with this immediate result, for in many earlier cases we found that the tumor had not been completely devitalized. We have therefore given supplementary doses of interstitial irradiation based on the original measurements of the tumor.

REPORT OF CASES

CASE 1.—*To illustrate the danger of reliance on external irradiation alone in the treatment for radiosensitive carcinomas of the breast.*

M. F., an Irish widow, aged 66, applied to the Memorial Hospital for treatment on Sept. 20, 1929, complaining of a lump in her right breast. Six children, the oldest of whom was 40 years of age, had been nursed for about eighteen months equally from both breasts. The patient had always been in good health except for pneumonia in 1926, and had entered the menopause at the age of 49. In the latter part of June, 1929, she felt a heavy lump in the upper outer quadrant of the right breast. This tumor gradually increased in size, causing pain, and on August 19, the overlying skin was red and inflamed. The patient was an elderly obese woman weighing 170 pounds (77.1 Kg.). Her lungs and heart were normal. Both breasts were large and pendulous. In the upper outer quadrant of the right breast was a large mass measuring 7 by 6.5 cm. The skin over the tumor, which was adherent and protruded in a moundlike eminence 2 cm. in diameter, was red, tender, inflamed and about to ulcerate. Several lymph nodes were palpable in the right axilla. A roentgenogram of the chest was negative for pulmonary metastases. The clinical diagnosis was primary operable carcinoma of the right breast with axillary metastases.

Treatment was given entirely by the radium element pack at 6 cm. distance. From September 29 until November 7, 16,000 milligram hours of treatment were given to the right axilla and an equal amount to the right supraclavicular space; 24,000 milligram hours were given to the right breast directed toward the tumor. The isodosis curve for the radium element pack at 6 cm. focal distance was such that we have computed the tissue dosage in the depth of the tumor as only 40 per cent of an erythema dose. The superficial portion of the tumor mass received one and one-half erythema doses. On December 2, the tumor and axillary nodes could no longer be palpated.

Comment.—An unusual instance is recorded of the complete clinical disappearance of a bulky mammary carcinoma, following one cycle of treatment with the radium element pack. The degree of radiosensitivity was comparable to that of many lymphosarcomas. Another unusual feature was the presence of a rapidly growing, highly radiosensitive mammary cancer in a woman of 66 years. Most mammary cancers in older women are slow growing and radioresistant. In estimating the tissue dose of any particular tumor, we consider the smallest amount of radiation which is delivered to any part of the tumor, in this instance 40 per cent of an erythema unit. This result is an excellent example of the so-called "selective cytolethal action" of the gamma rays of radium. What should be the future management of such a patient who is clinically free from disease? Experience taught us that the previously mentioned treatment was insufficient to prevent a recurrence. With only external irradiation to rely on, the interval of time between treatments would be long enough to permit any surviving cancer cells to acquire radioresistance, and the amount of irradiation would be definitely limited by the tolerance of the skin over the tumor. Since this tumor was probably highly malignant, as judged by its radiosensitivity, a radical mastectomy without preoperative irradiation would probably be accompanied by the hazard of widespread dissemination of cancer cells.

Subsequent Irradiation.—In agreement with our previous statements, we believed the safe amount of radiation to employ to be that which is capable of destroying the most radioresistant cancer; therefore on Jan. 17, 1930, 86 millicuries of radon in 30 gold seeds and 30 millicuries in 11 gold seeds were implanted in the breast and axilla, respectively. This afforded a dosage of 12 skin erythema units to the

mammary tumor; the calculation was based on the original measurement of the tumor, and the gold seeds were inserted in the breast at the site which the tumor occupied. On February 7, only three weeks following interstitial irradiation, a right radical mastectomy was performed. Residual carcinoma of the breast was found on microscopic examination; the carcinoma was so necrotic and affected by radiation that its type could not be determined. There were areas of hyaline tissue with true bone formation in the tumor; hydropic degenerated tumor cells were found in the interstices of the diseased tissue. These observations were considered indicative of metaplasia occurring in regressing cancer.

Final Comment.—The presence of cancer in the amputated breast following heavy interstitial irradiation (1,200 per cent S. E. D.) and the clinical disappearance of such a cancer following external irradiation only (40 per cent S. E. D.) indicate the wide range in radiosensitivity of the cells comprising this tumor.

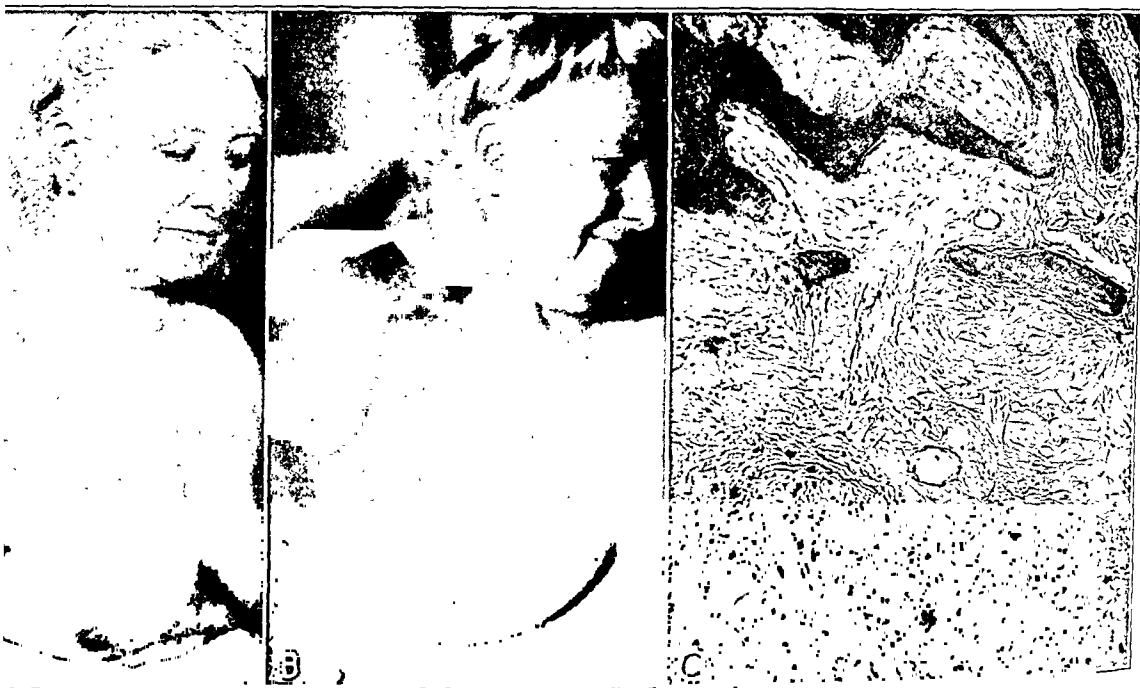


Fig. 7.—(A) Carcinoma of the axillary segment of the right breast. Measurement of neoplasm, 7 by 6.5 cm. (B) Complete clinical disappearance of the cancer following treatment by the radium element pack. (C) Hyaline tissue, true bone formation (metaplasia) and remnants of hydropic tumor in regressing mammary cancer.

Another principle is illustrated here, namely, the employment of a dose of interstitial irradiation based on the original measurement of the large tumor which had completely disappeared following external irradiation. This principle should be applied cautiously for fear of radium necrosis. The patient is at present clinically free from disease, and the wound is well healed. Primary wound healing did not occur after mastectomy, owing to the short interval between the interstitial radiation and operation (three weeks). (See fig. 7.)

The tissue dose delivered to the tumor should always be measured and expressed in skin erythema units. This dose should be prescribed. The tables prepared in the physical department enable the clinician to

translate into terms of skin erythema units the tissue dose delivered either by external or interstitial irradiation.

Method of Measuring a Mammary Tumor.—With the patient in the recumbent posture, the transverse and vertical contours of the involved breast at the level of the tumor are taken by the adjustment of flexible lead tapes, later tracings being made on paper for permanent record. The tumor of the breast is measured in its three dimensions by calipers calibrated in centimeters. The exact location and size of the tumor are recorded on the traced contour of the breast, care being taken to show the exact depth below the level of the skin. This graphic record is used for estimating the amount of radiation delivered from external sources to the most remote portion of the tumor.

CASE 2.—To illustrate the control of mammary cancer by the use of external and interstitial irradiation.

O. R., an English woman, aged 57, married, applied to the Memorial Hospital in May, 1920, complaining of the presence of two small lumps in her right breast. In 1893, she had had one child whom she had nursed for five months; she had had no lactational difficulties. In March, 1920, a hysterectomy was done for fibromyoma. For two years, she had been aware of two small lumps in the right breast. This breast had undergone gradual atrophy, and the tumors were slightly painful. In the upper inner quadrant of the right breast was a small horseshoe-shaped mass, measuring 5 by 3 cm. It was definitely adherent to the superjacent skin. There were no palpable axillary or supraclavicular lymph nodes. A roentgenogram of the chest was negative for pulmonary metastasis. The clinical diagnosis was primary operable carcinoma of the breast.

Immediate treatment was instituted, a low voltage roentgen cycle to the right breast and drainage areas being employed from May 29 to June 9. On August 13, a biopsy was performed on the residual tumor of the right breast. Microscopic study of this specimen by Dr. Ewing revealed carcinoma simplex. Three additional low voltage roentgen cycles were given to the right breast and drainage areas in September and November, 1920 and in March, 1921, respectively. Dr. Frank E. Adair then gave interstitial irradiation in glass radon seeds. On Feb. 14, 1931, the patient was without clinical evidence of cancer. She has remained in excellent health for twelve years from the known date of onset, and ten and one half years from the first treatment given at the Memorial Hospital. The administration of four cycles of roentgen treatments in the course of ten months caused marked telangiectasia and sclerosis of the skin of the breast.

Comment.—The prolonged survival of this patient without clinical evidence of cancer does not indicate that a cure has been obtained. We believe that we have been successful in the production of abortive fibrosis to such a degree that the residual mammary cancer is perhaps permanently entombed in scar tissue within the breast. The depth of the dose of irradiation delivered by these roentgen treatments is insufficient to destroy the average radioresistant mammary cancer, but it can induce marked fibrosis of a cancer bed; for practical purposes this result might be considered as equivalent to a cure. (See fig. 8.)

We shall give a summary of the steps in the calculation of the tissue dose when treatment has already been given.

A. External Radiation

1. Calculate the percentage erythema dose on the skin for each treatment.
2. Determine the distance from the depth of the tumor mass to the center of each portal on the skin.

3. From the proper curve for the depth dosage determine the percentage of surface radiation delivered at the given depth for each treatment.
4. Multiply this percentage for each treatment by the percentage given in 1. This gives the tissue dose for each treatment.
5. Add results given by 4 for all external treatments.



Fig. 8.—(A) Carcinoma of the upper central segment of the right breast. (B) Telangiectatic mammary skin eight years following low voltage irradiation. (C) Photomicrograph of the specimen taken for the original biopsy; carcinoma simplex.

B. Interstitial Radiation

1. Determine the three dimensions of the tumor mass.
2. Decide what sphere or group of spheres define it.
3. (α) For a single sphere the diameter of which is the largest dimension of the mass, by means of the figures in the column for this diameter in the table for gold seed doses, determine the tissue doses by the number of millicuries used.

(b) For a group of spheres, divide the total number of millicuries by the number of spheres; then in one sphere, determine the dose as in *a*. This is the tissue dose from interstitial radiation.

C. Add the results of *A* 5 and *B* 3 for the total tissue dose.
This is the minimum dose delivered in the tumor mass.

We shall now give a summary of the steps in the calculation of the radiation necessary to give a specified tissue dose.

1. Specify the tissue dose to be given (the minimum).
2. Decide what external treatment is advisable.
3. Determine the distance from the depth of the lesion to each portal in the skin for external radiation.
4. Calculate the tissue dose from this external radiation as in the case for treatment already given. (See the preceding outline, sections *A* 3 and 4).
5. Subtract the tissue dose thus obtained from the specified dose. The remainder is to be given by interstitial radiation.
6. Determine the three dimensions of the lesion.
7. Decide what sphere or group of spheres to consider as defining it.
8. (a) For a single sphere the diameter of which is the largest diameter of the mass, determine the number of millicuries necessary to give the dose specified in 5. This diameter will be found in the table for gold seed doses.
(b) For a group of spheres, determine the number of millicuries necessary to give the dose specified in 5 from data found in the column for the diameter of one sphere of the group. Multiply this by the number of spheres. This gives the dose of interstitial irradiation required.

The mammary gland will tolerate safely an enormous dose of interstitial irradiation. The first time 40 millicuries were introduced into the breast, we were somewhat fearful of the consequences. As no untoward effects were evident, the number of millicuries was cautiously increased until as much as 133 millicuries were given in gold seeds. The degree of radium reaction in the breast is proportionate to the amount of interstitial irradiation, but even a large amount is insufficient to injure seriously the skin of the breast. Small breasts are given less interstitial treatment. One should bear in mind that radon implanted in a breast irradiates in all directions. In the estimation of the required dosage, care should be exercised to avoid a possible permanent injury to the wall of the chest or underlying pleura by overdosage, especially when the tumor is contiguous to the ribs. We have not observed pleuritis as a complicating sequel to these treatments.

CASE 3.—To illustrate the great tolerance of the mammary gland for interstitial irradiation.

M. P., a white woman, aged 48, married, applied to the Memorial Hospital on Feb. 25, 1930, complaining of a lump in the left breast. She had had one miscarriage but no other pregnancies. In 1930, she had had a hysterectomy for pelvic inflammatory disease. Fifteen months prior to admission, she fractured her left wrist and traumatized her left breast by a fall. In November, 1929, she first noticed a tumor in the upper inner quadrant of the left breast. Since then there

had not been any change in the size of this tumor, mastalgia, secretion from the nipple, loss of weight or cough. On physical examination, a tumor 6.5 by 5 by 3 cm. was found to occupy the upper inner quadrant of the left breast. Both breasts were large and pendulous. The skin over the tumor was definitely adherent. There were no palpable lymph nodes in the axilla or supraclavicular spaces. A roentgenogram of the chest was negative for pulmonary metastases. The clinical diagnosis was primary operable carcinoma of the left breast.

On Feb. 27, 1930, 133 millicuries of radon in 40 gold seeds were inserted into the tumor, constituting a tissue dose of 2,070 per cent S. E. D. External irradiation was not given. The tumor disappeared in two months after treatment, but the excoriation of the skin was slow in healing. On June 26, three and one half months after irradiation, a left radical mastectomy was performed. On section of the breast, the tumor had diminished markedly in size; it measured 2 by 1.5 by 1.5 cm., and was completely necrotic. The axillary lymph nodes were not involved. Microscopic examination showed the tumor to be a carcinoma simplex that had undergone complete radium necrosis. The wound healed well with the exception of slight necrosis along the line of incision. On Jan. 26, 1931, there was no clinical evidence of cancer; the wound had healed well without inflammation or necrosis.

Comment.—This patient accidentally received twice the dose considered necessary to sterilize the cancer. The large size of the breasts and the abundance of enveloping fatty tissue account in large part for the tolerance of this breast to such an enormous dose of irradiation. Of equal interest is the fact that the healing of the wound after wide radical mastectomy was only slightly impaired.

In radiation therapy, the dose is usually dependent on the relative susceptibility of the cancer and the normal environmental tissues, e. g., the therapeutic index equals $\frac{\text{susceptibility of normal tissue}}{\text{susceptibility of tumor}}$. Fortunately, we have seen that the breast will safely tolerate sufficient interstitial irradiation to destroy the most radioresistant mammary cancer. On the basis of our histologic studies of amputated breasts as treated, we now believe that the tissue dosage necessary to effect destruction of a radioresistant mammary cancer, approximates twelve erythema doses. It is true that sufficient time has not elapsed to estimate the sterilizing dose for mammary cancers treated by irradiation without subsequent mastectomies. Although mammary cancers vary considerably in radiosensitivity, we believe that the safest procedure is to treat all with the same sufficient dose, because radiosensitivity cannot always be determined before operation, and the same tumor may contain radioresistant and radiosensitive portions.

As can be seen in table 5, many of the carcinomas received supra-lethal doses. When the tumor mass is small an overdose of interstitial irradiation may safely be given; this is usually done intentionally. If the tumor is 3 cm. in diameter, the dosage may be planned for a mass 5 cm. in diameter, thereby irradiating heavily the all-important, growing edge of the cancer.

Whenever the carcinoma has been destroyed with complete regression of the palpable mass and satisfactory repair, we assume that the dose has been optimum. If radionecrosis and destruction and ulceration of the skin follow (of which we have observed only one instance), we consider the dose as excessive. If the cancer almost disappears but later resumes its growth activity, we know that the dose has been inadequate. If there has been no measurable diminution in the size of a mammary cancer that received the maximum tissue dose from preliminary external irradiation, we are dealing with a radioresistant carcinoma. If the carcinoma diminishes markedly in size and remains indefinitely as a firm,

TABLE 6.—*Efficient Doses of Irradiation for Primary Carcinomas of the Breast*

Skin Erythema Doses	Sublethal Doses	Lethal or Supra-lethal Doses
1.....	6	..
From 1 to 2.....	9	2*
From 2 to 3.....	1	..
From 3 to 4.....
From 4 to 5.....
From 5 to 6.....
From 6 to 7.....	2	..
From 7 to 8.....	2	..
From 8 to 9.....	1	2
From 9 to 10.....	3	3
From 10 to 11.....	1	2
From 11 to 12.....	..	4
From 12 to 13.....	..	4
From 13 to 14.....	1†	2
From 14 to 15.....	1‡	..
From 15 to 16.....	..	1
From 16 to 17.....	..	1
From 17 to 18.....	..	1
From 18 to 19.....	..	1
From 19 to 20.....	..	3
20+.....	..	2

* In two radiosensitive carcinomas, mastectomies were not performed. Clinical evidence of cancer was not present after one and two years, respectively.

† Improperly placed gold seeds.

‡ The breast was amputated less than four weeks after the insertion of gold radon seeds.

inactive mass, we realize that we have attained abortive fibrosis and restraint of the growth of the tumor, which is the object of an inhibitory dose.

CASE 4.—*To illustrate the present method of treating patients for mammary cancer by external and interstitial irradiation followed by radical mastectomy.*

E. P., a white woman, aged 46, married, applied to the Memorial Hospital on May 10, 1929, complaining of a large lump in the left breast. She had three children, aged 23, 21 and 18 years. Following the birth of the first child, her left breast became caked. When this subsided, a residual lump remained which had begun to increase in size during the past few months before admission. In the upper outer quadrant of the left breast was a bulky, firm tumor measuring 5.5 by 3-by 3 cm. The tumor was firmly adherent to the overlying skin. There were many large palpable lymph nodes in the left axilla. The clinical diagnosis was primary operable carcinoma of the left breast with axillary metastases.

Immediate treatment was instituted by giving 16,000 milligram hours by the radium element pack at 6 cm. distance over the left breast (May 29, 1929). On

July 10, this was followed by the implantation of 18 gold seeds totaling 41.15 millicuries, in the tumor of the left breast, and the insertion of 3 platinum filtered needles totaling 159 millicuries for a dosage of 700 millicurie hours in the left axilla. Five and one half weeks later, on August 20, a left radical mastectomy was done. The wound healed by primary intention. The tumor received slightly more than 9 skin erythema doses of irradiation. On microscopic examination, a very cellular carcinoma was recognized, but it was too necrotic to classify or grade. No viable carcinoma was seen anywhere. There was some squamous metaplasia of the ducts. At the last examination, on Feb. 18, 1931, there was no evidence of recurrence.

Comment.—The tissue dose of 940 per cent S. E. D. delivered by combined external and interstitial irradiation was sufficient to destroy completely a cellular carcinoma of the left breast. (See fig. 9.)



Fig. 9.—(A) Carcinoma of the upper outer quadrant of the left breast. (B) Postoperative view of patient showing integrity of skin and character of wound healing. (C) Complete necrosis of a very cellular mammary carcinoma (table 9, case 8).

CASE 5.—*To illustrate the present method of treating patients for mammary cancer by external and interstitial irradiation followed by radical mastectomy.*

M. Z., a Russian woman, aged 38, married, applied to the Memorial Hospital on Sept. 4, 1929, complaining of pain in her right breast and the presence of a lump in her right armpit. She had been pregnant only once, for which a cesarean section had been performed; the child was stillborn. She detected the lump in her right axilla only three days before application to the Memorial Hospital. In the central portion of the right breast posterior to the nipple was an irregular tumor measuring 6 by 6 by 4 cm. The nipple was retracted and fixed. The skin of the areola was adherent to the tumor. A node 2 cm. in diameter was situated in the lower part of the right axilla. A roentgenogram of the chest was negative. The diagnosis was operable carcinoma of the right breast with axillary metastasis.

Preliminary treatment was instituted by giving a high voltage roentgen cycle to the right breast and drainage areas (from September 4 to 16). This was followed on September 21 by the implantation of 49.38 millicuries of radon in 14 gold seeds into the tumor of the right breast. Four weeks later, on October 18, a right radical mastectomy was performed. The wound healed by primary intention. In the sectioned breast, the tumor was surrounded by a hemorrhagic, necrotic zone of tissue. Histologically, there was marked productive fibrosis, profound metaplasia of the ducts, and marked, practically complete, necrosis, of the tumor, which was an infiltrating duct carcinoma. The metastatic carcinoma in the axilla and lymph node was also largely destroyed. At the time this article was written, sixteen months later, there was no evidence of recurrence.

Comment.—A tissue dose of 1,020 per cent S. E. D. delivered by combined external and interstitial irradiation was sufficient to produce marked necrosis and productive fibrosis in an infiltrating carcinoma of the breast. (See fig. 10.)

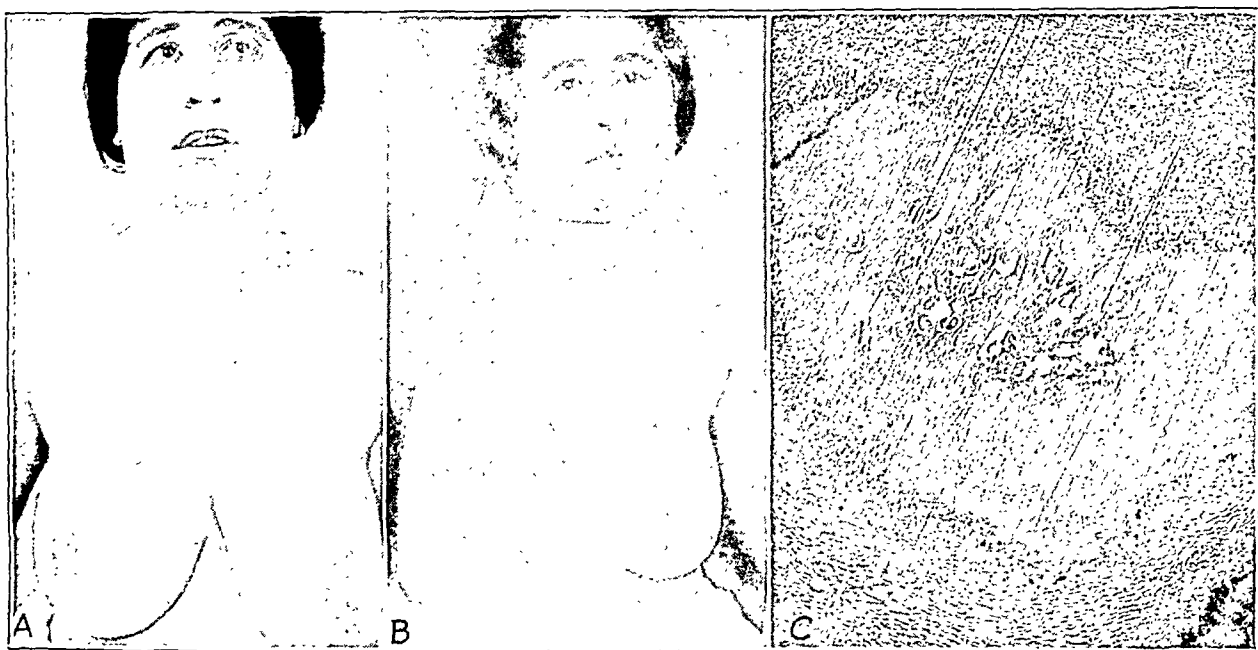


Fig. 10.—(A) Carcinoma of the central part of the right breast. (B) Post-operative view of patient showing integrity of skin, character of the wound healing and maintenance of good function in the arm. (C) Photomicrograph showing marked necrosis of duct carcinoma (table 10, case 5).

IRRADIATION OF THE AXILLA

The axilla is irradiated whether or not axillary nodes are palpable, for we have shown that there is a possibility of error of 17 per cent in determining the presence or absence of involved axillary nodes. The axillary is irradiated by preoperative roentgen rays or radium element pack followed by interstitial gold-filtered radon distributed along the gland-bearing areas. In general, we have found the management of axillary nodes one of the big problems in the treatment for mammary cancer by radiation, and we believe that our present means of attack is not wholly satisfactory.

The axillary nodes are variable in their distribution and cannot be accurately localized at fixed anatomic points. Ewing has said, "Unlike cervical lymph nodes, axillary nodes may lack complete capsules and are readily traversed by tumor cells." The dispersion of active carcinoma cells in the axillary fat seriously hinders the cure of cancer in this location, for these cells divide rapidly in spite of heavy external irradiation. As long as the cancer cells remain within the node, external irradiation has a perceptible influence because of the pressure atrophy, vascular occlusion with ischemia, and strangulation. The difficulties attendant on estimation of depth dosage from external radiation are several. The axilla is a truncated cone or rather an equilateral four-sided pyramid, which varies in shape and depth in different persons. A certain amount of radiation reaches the axillary contents from the treatments given over the corresponding supraclavicular space. When multiple metastases to several axillary nodes have occurred, the correct estimation of the tissue dosage for these nodes is impossible. When one or two, quite large, movable nodes are present, the tissue dose can be calculated and delivered with considerable ease.

External irradiation alone is inadequate in the treatment for carcinomatous metastases to the axilla, as it is in that for carcinoma of the breast. Interstitial irradiation must be employed if metastases are present. The introduction of gold radon seeds into small axillary nodes has turned out to be a difficult matter, for without opening the axilla, one cannot accurately localize the nodes at the time of introduction, and satisfactory implantation may be impossible. On opening the axilla in the endeavor to isolate nodes, we frequently find that it is easier to dissect out fat and nodes than to attempt to introduce radium into separate nodes. Whenever the nodes are large, the radon can be introduced easily into their substance without surgical exposure (table 13, patient E. H.). The gold seeds are implanted in the axilla at the same time and with the same technic as they are in the breast. Rows of gold seeds are placed along the lymphatic trunks leading to the axilla and along the important intermuscular trunks. Stronger gold seeds are deposited in the region of the pectoral group of nodes along the inferior posterior aspect of the pectoral muscles, adjacent to the anterior insertion of the latissimus dorsi, and in the region of the subclavicular group, a most important region, as these nodes are the immediate relay stations prior to involvement of the supraclavicular nodes. The former nodes are reached by transfixion of the axillary skin, whereas the needles are inserted into the latter region by a row of transcutaneous punctures below and parallel to the outer half of the clavicle. While the needle points are guided into the apex of the axilla by careful palpation, the left hand pushes the axillary vessels high out of harm's way. The gold radon seeds should

never be placed nearer than 1 cm. to the branches of the brachial plexus. otherwise intractable neuritis may ensue. No edema of the arm has ever followed these treatments. The axillary fat becomes drier than normal, and there is some fibrosis, but these changes do not handicap subsequent axillary dissection.

CASE 6.—*To illustrate the necessity of interstitial irradiation of carcinomatous metastases to the axillary lymph nodes.*

S. Z., a Polish woman, aged 34, married, applied to the Memorial Hospital on Dec. 29, 1928, complaining of a lump in her left arm pit. Menstruation had always been normal. She had four children, aged from 5 to 14 years, whom she

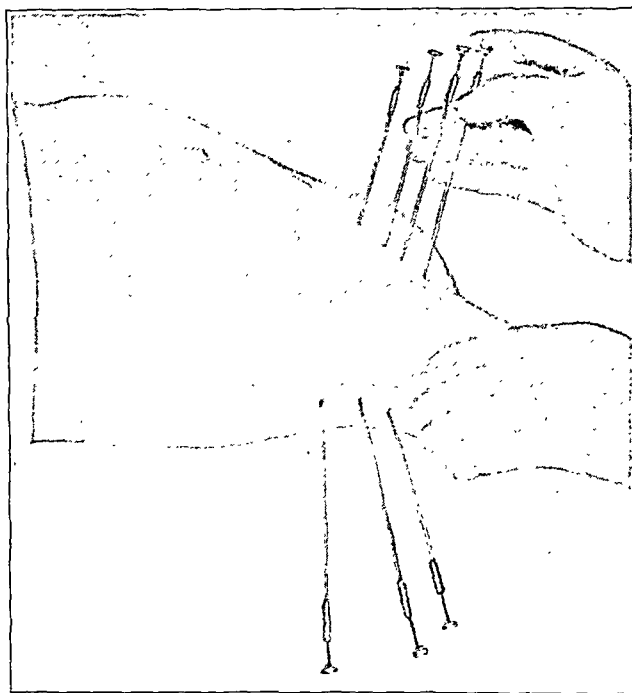


Fig. 11.—Technic of implantation of gold radon seeds in the left axilla.

had nursed for from fourteen to eighteen months without lactational difficulties. On Oct. 1, 1928, she accidentally felt a lump, the size of a hen's egg, in her left axilla. There had never been any mastalgia, discharge from the nipple, loss of weight, dyspnea or cough. On physical examination, there was chloasma and slight hypertrophy of the thyroid gland. The external and internal genitalia were apparently normal. The right breast was clinically free from disease. In the lower outer quadrant of the left breast were two, small, barely palpable nodules, about the size of a hazelnut. In the left axilla were five or six large, discrete, hard lymph nodes, measuring 5 cm. in diameter. A small lymph node in the left supraclavicular space was thought to contain metastatic carcinoma. The clinical diagnosis was inoperable carcinoma with metastases to the axillary and supraclavicular lymph nodes.

Immediate treatment was instituted, employing a high voltage roentgen cycle to the left breast and drainage areas (from December 31 to Jan. 7, 1929). This was followed by radium element pack treatments, 14,000 milligram hours at a

distance of 6 cm., to the left axilla and left supraclavicular space (from January 19 to January 27). By August, the supraclavicular node was no longer palpable; the axillary nodes were still very large and hard, and the nodules in the breast were unchanged. At this time, 21.3 millicuries of radon in 10 gold seeds were implanted in the left axilla; the tiny nodules in the breast likewise received interstitial irradiation (ten skin erythema doses). By October, the mammary and axillary tumors had disappeared; there had been no recurrence to Feb. 12, 1931. She experienced amenorrhea from November, 1929, to February, 1930, at which time a large left ovarian tumor was recognized as complicating pregnancy. At laparotomy, a panhysterectomy was performed. The left ovary was 15 by 10 cm. in diameter; the microscopic diagnosis was metastatic tubular carcinoma of the type in the breast. The patient had had no clinical evidence of cancer to Feb. 12, 1931.

Comment.—The bulk of the axillary metastases and the small size of the primary cancer in the breast led us to believe that the neoplasm was anaplastic. This carcinoma was sufficiently radioresistant to be refractory to external irradiation. We expect the late appearance of other metastases, although a year has elapsed since the last metastasis (ovarian) was treated. External irradiation obviously could not deliver a lethal dose into the substance of the axillary tumor, which was apparently accomplished by the implantation of gold radon seeds.

Unfiltered Interstitial Irradiation.—In the early part of the last decade, radon was collected in tiny glass capillary tubes, which were subdivided into shorter segments called "bare glass radon seeds." For the treatment for carcinoma of the breast, these glass-filtered radon implants were inserted interstitially to deliver a dosage of approximately 1 millicurie for each cubic centimeter of tumor tissue. The general tendency was to give repeated treatments in small doses. The glass wall of the capsule filtered out the alpha rays and some of the soft beta rays, but sufficient of the latter escaped to exert a caustic action on the tissue surrounding the seeds. Enveloping each glass seed was a sphere of coagulation necrosis which in turn was surrounded by an outer zone of nonviable but recognizable carcinoma. The beta rays were stopped by the carcinoma, but the more penetrating gamma rays extended farther peripherally to sterilize a still larger sphere of tissue. These "bare glass seeds" produced much more necrosis than occurs from gold-filtered implants. The sequence of events in the irradiated breast was carbonization, colliquation and dense fibrosis. Dr. Ewing, who studied these histologic changes with the microscope, has long maintained that the glass-filtered radon seeds are superior to gold seeds for interstitial irradiation of the breast.

Radium Puncture by Platinum-Filtered Needles.—In 1920, we first employed hollow, radon-containing needles for interstitial irradiation of mammary cancer. Each needle had a steel shank from 8 to 10 cm. long, to which was attached a platinum point 4 cm. long, with a wall 0.4 mm. thick. Into the platinum tip from 60 to 80 millicuries of radium emana-

tion were introduced and sealed with paraffin. The needles were sterilized by immersion in alcohol. The longitudinal and transverse diameters of the tumor having been determined by caliper measurement and the average thickness estimated, the cubic contents were calculated. At first, the dosage used was 25 millicurie hours per cubic centimeter; later the dosage was increased to 50 millicurie hours per cubic centimeter of tissue. Under procaine hydrochloride anesthesia, we passed the needles through the skin and into the tumor along two peripheral transverse lines, endeavoring to place them equidistant from the anterior and posterior surfaces. Now that we have available more accurate data concerning cancericidal doses of radium, we can appreciate in retrospect the remarkably good results obtained with these radon needles in consideration of the dose delivered. One serious objection to their usage was the attendant trauma. The needles were also directed subpectorally toward the axillary apex and downward into the axilla from the infraclavicular region.

Another device for this method of treatment is the employment of hypodermic needles of lengths suited to the size of the tumor; the lumina of these needles are threaded with gold radon seeds in tandem formation, and the ends of the needles are plugged with soft wax. These needles may be used to perforate the tumor in various directions.

CASE 7.—To illustrate the interstitial use of platinum-filtered radon needles.

S. S., a Russian woman, aged 41, married, applied to the Memorial Hospital on June 20, 1925, complaining of a lump in the upper outer quadrant of the right breast. In 1907, she gave birth to a child whom she did not nurse. The lump in the breast had been present for eighteen months and had gradually increased in size. On physical examination, the tumor measured 6 by 3 by 3 cm., was ovoid in shape and adherent to the superjacent skin. There were small palpable nodes in the axillae, which were not considered neoplastic. A roentgenogram of the chest was negative for pulmonary metastasis. The diagnosis was primary operable carcinoma of the right breast.

In June, 1925, four platinum-filtered needles, containing a total of 92 millicuries, were inserted through the tumor of the breast for six and a half hours. This was preceded by a low voltage roentgen cycle of irradiation to the right breast and drainage areas. In July, a right radical mastectomy was performed. Five centimeters from the nipple was an indurated area 2 cm. in width, in which small necrotic foci were evident. There was considerable chronic inflammation in the fatty tissue and some liquefaction necrosis. There was no macroscopic evidence of cancer; microscopically, however, a small cell, anaplastic, infiltrating carcinoma was found to be markedly injured by the irradiation and enclosed in scar tissue. Amputation of the breast was followed by two postoperative low voltage roentgen cycles in the following October and in August, 1926. At the last examination, on Jan. 19, 1931, there was no evidence of cancer. There was some lymphedema of the right arm and hand.

Comment.—Considering the very small dose of radiation delivered into this tumor, the histologic effect on the cancer and the subsequent freedom from disease are quite satisfactory. The pathologic findings indicated the possibility of complete destruction of mammary cancer by heavier interstitial irradiation.

CASE 8.—To illustrate the treatment for primary operable mammary cancer by external irradiation supplemented by interstitial radiation in the form of platinum-filtered radon needles.

R. O., a Norwegian woman, aged 43, married, applied to the Memorial Hospital on Nov. 14, 1924, complaining of a lump in the right breast. She had had one child in 1916 whom she had nursed without lactational difficulties. Two days prior to admission, she accidentally discovered a painless lump in her breast. This lump involved the upper outer segment, and was adherent to the superjacent skin. There were no palpable lymph nodes in the axilla or supraclavicular space. A roentgenogram of the chest was negative for pulmonary metastases. The diagnosis was primary operable carcinoma of the breast.

In December, two platinum-filtered radon needles were inserted in the right breast for a dosage of 480 millicurie hours. This treatment was preceded by a

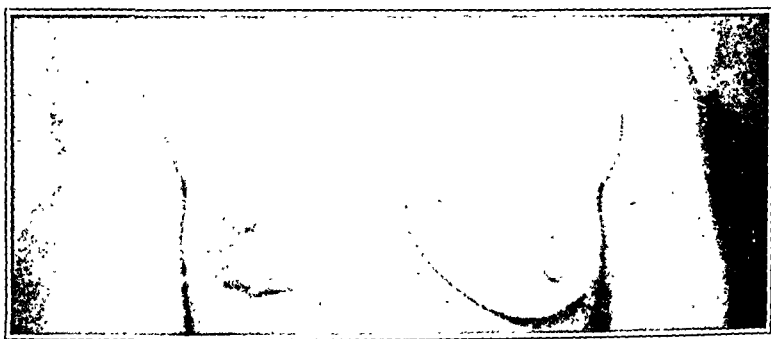


Fig. 12 (case 8).—Appearance on March 10, 1930, of carcinoma of the right breast treated in 1924 by interstitial platinum-filtered radon needles.

low voltage roentgen cycle to the right breast and drainage areas. In March, 1925, two platinum-filtered radon needles were inserted into the tumor of the breast for a dosage of 420 millicurie hours. This treatment was followed by another low voltage roentgen cycle to the right breast. In March, 1926, a radon tray, at a distance of 3 cm., was applied over the mammary tumor for a dosage of 3,000 millicurie hours. In the following June, an additional low voltage roentgen cycle was given to the right breast. In September, seven platinum-filtered radon needles were inserted into the right breast for a dosage of 1,160 millicurie hours. During this time the lump in the breast regressed gradually in size; a small fibrosed nodule remained which was considered to be either scar tissue or residual tumor. In 1927, the right axilla received 30,000 millicurie hours at a distance of 6 cm. with 2 mm. of brass filter, by a radon emanation pack of 70 sq. cm. surface-radiating area. The patient has remained in excellent health without clinical evidence of carcinoma. (See fig. 12.)

Comment.—External irradiation together with interstitial irradiation by means of radon needles can suffice to treat mammary cancer which is confined to the breast. The proper dosage for this method of treatment is difficult to estimate and therefore somewhat empiric.

A CRITIQUE OF KEYNES' METHOD OF IRRADIATING CARCINOMA
OF THE BREAST

More recently Keynes has placed needles of variable length and of variable content of radium element in the breast proper, the axilla, beneath the pectoralis major muscle, above the clavicle, below the clavicle and over the first three or four intercostal spaces. These needles are left in place for five days. Allowing for the relatively recent period in which this work was done, Keynes has secured encouraging results with his technic. By April, 1929, he had subjected ninety patients to this procedure. In the first fifty cases, biopsy was done at the time the needles were removed. Since this time he has relied on the accuracy of his clinical diagnosis for statistical data. On several occasions, a nodule of carcinoma developed in the scars of the biopsy even though irradiation was in progress. We commend the principles underlying this technic of interstitial irradiation, but find certain objections to the assumptions made concerning its effectiveness. The computation of correct tissue dosage by this method is very difficult because the distribution of the radon in the needles does not constitute point sources for calculation. In only a few cases did Keynes excise the irradiated tumor; the remaining breasts were left intact, so that now no one knows whether the carcinomas were destroyed completely or are viable and latent in the deep scars within the breasts (abortive fibrosis). In his three available papers, he cited the same two cases wherein postradiation excision was performed; the dosage was said to be inadequate because carcinoma was found in each specimen, although one of these patients has remained clinically free from cancer for over five years. Our own experience has taught us not to rely on the clinical disappearance of the carcinoma thereby leaving the breast in situ, but (until a safe dose is determined) to amputate these irradiated breasts and to ascertain the dosage that affords microscopic evidence of complete destruction of the cancers. The results by any other method must be attained by trial and error.

THE INFLUENCE OF PREOPERATIVE IRRADIATION ON WOUND HEALING

The influential factors in wound healing following radical mastectomies for carcinomas of the breast that have been treated preoperatively by irradiation are several: (a) The presence of an open, infected lesion as a source of wound contamination; this same hazard obtains in non-irradiated cases, but is of more serious import here because of the tenacity with which infection persists in irradiated tissues. (b) The adiposity of the breast and the axilla influence healing; wound healing in obese patients is difficult in the best circumstances, but in irradiated fatty tissue the process is even slower. (c) The size of the tumor, especially in comparison with the size of the breast. (d) The amount

of skin sacrificed and the consequent degree of tension; with the progress of time, the vascularity of irradiated skin gradually diminishes, a condition that impedes wound healing. (e) The employment of external irradiation; all other conditions being equal, the tissue dosage delivered by external irradiation through the skin to the tumor, provokes far greater injury to the skin than an equivalent dosage given interstitially. (f) The use of interstitial irradiation and the total quantity of radium emanation employed. The dosage of interstitial irradiation should be limited by the size of the breast. This problem has been readily solved and is dependent somewhat on the relation of the size of the tumor to that of the breast that contains it. When a bulky carcinoma occupies almost the entire breast, a lethal dose of interstitial irradiation may destroy the skin, produce ulceration, delay amputation and impair the healing of the wound. (g) The proximity of the gold radon seeds to the wall of the chest. If the carcinoma is situated deeply in the breast, in contact with the thoracic wall, care must be exercised in the dosage and placement of the gold radon seeds, otherwise late radiation effects even pleural, periosteal or perichondrial damage, and tardy bone necrosis may ensue. (h) The time interval between the completion of the irradiation and the operation. This is evidently the most important factor. The allowance of an optimal interval diminishes the risk of infection, permits the subsidence of the inflammatory reaction in the skin of the breast, affords the necessary time for destruction of the tumor by irradiation, gives the deeper substance of the breast and contiguous tissues an opportunity to recover from the intense reaction to the radium, and thus insures uncomplicated wound healing. From six to ten weeks should elapse following interstitial irradiation before radical amputation. When the operation is done sooner, additional hemostasis is necessary because of the post-radiation hyperemia present, and the fresh wound shares in the tissue destruction. When the operation is performed some months after massive overirradiation, the consequent fibrosis and ischemia frequently hinder the process of repair in the wound.

In an analysis of the cases of delayed or secondary wound healing, we have perceived that the interval of time between heavy irradiation and operation was short, with one exception, in which the dosage was too large for the size of the breast.

- Case 1, table 11, 635 per cent S. E. D. Interval of 29 days.
- Case 2, table 11, 650 per cent S. E. D. Interval of 36 days.
- Case 2, table 9, 1,000 per cent S. E. D. Interval of 20 days.
- Case 8, table 13, 1,000 per cent S. E. D. Interval of 27 days.
- Case 9, table 11, 1,200 per cent S. E. D. Interval of 21 days.
- Case 6, table 9, 1,500 per cent S. E. D. Interval of 36 days.
- Case 17, table 13, 2,150 per cent S. E. D. Interval of 44 days.

TABLE 1.—Patients with Primary Operable Carcinoma of the Breast Treated by Roentgen Rays

Patient	Age	Loca- tion of Tumor, Size	Rate of Growth	Axilla* Adenopathy	Clinical Index of Malignancy	Operation	Healing of Wound	Roentgen Treatments	Doses per Cent., Interval Between Breast, Irradia- tion	Tissue Interval	End-Result	Gross Pathologic Anatomy	Pathologic Histology
L. W.	51	Left, 3.75×2.5 cm.	Rapid	Adenopathy	B	2/10/28, radical mastectomy	Slough	1/13/28, 2 low voltage treatments	100	4 wk.	Metastases to the lungs	Tumor, 1×1 cm.	Carcinoma simplex; fibrosis; slight atrophy of tumor cells; invasion of lymphatics; mucinous changes in stroma
L. R.	46	Left, 9×6 cm.	Rapid	Adenopathy	B+	None	1/10/28, 2 low voltage treatments	100	2/26/28, died	Carcinoma simplex, grade 2 radioresistant; abortive fibrosis as result of local vascular change; bulk of tumor relatively unaltered
B. M.	71	Left, 4.75×3.5 cm.	Slow	0	A	12/16/27, local mastectomy	Primary healing	11/18/27, low voltage heavy treat- ments	110	4 wk.	8/15/29, died from cardiac failure; no cancer	Carcinoma simplex, grade 2 radioresistant; abortive fibrosis as result of local vascular change; bulk of tumor relatively unaltered
T. S.	42	Right, 4.25×2.5 cm.	Slow	Adenopathy	B	6/23/28, radical mastectomy	Good heal- ing	5/29/28, 2 high voltage treatments	130	1 mo.	No evidence	Tumor, 1.5×1 cm.	Adenocarcinomatous foci in fibro-adenoma; axillary node carcinom- atous
Y. N.†	72	Left, 3.5×2.25 cm.	Slow	Adenopathy	B—	5/22/28, 2 high voltage treatments	130	No evidence	Evidently very radio- sensitive	Infiltrating adenocarci- noma; much fibrosis; viable tumor
L. F.	35	Right, 3.5×2.5× 2.5 cm.	Rapid	Adenopathy	O	6/23/28, radical mastectomy	Primary healing	5/23/28, 2 high voltage treatments	135	16 days	8/19/30, died; metastases to the lungs and bone	Tumor, 1.5 cm.	Gelatinous adenocarci- noma; slight atrophy of tumor cells; axillary node carcinomatous
E. D.	46	Right, 3.5×3.5 cm.	Rapid	Adenopathy	C—	1/27/28, radical mastectomy	Good heal- ing	1/17/28, 2 high voltage treatments	140	10 days	Metastasis to the skin, lung and skull	Tumor, 2×2 cm.	Adenocarcinoma, grade 2 radioresistant; marked fibrous tissue reaction
R. B.	45	Right, 5.5×3 cm.	Slow	Adenopathy	B—	6/22/28, radical mastec- omy	Slow healing at lower end of wound	5/29/28, 2 high voltage treatments	140	3 wk.	Cerebral metastases	Tumor, 5×5 cm.	Duct carcinoma with early infiltration; viable tumor, but atrophic and sloughing; fibrosis and calcification
K. C.	64	Right, 10×5×4 cm.	Rapid	Adenopathy	B+	7/20/28, radical mastectomy	Primary healing	5/22/28, 2 high voltage treatments	140	2 mo.	No evidence	Infiltrating tubular adenocarcinoma; consid- erable hydropic degenera- tion; axillary nodes free from cancer
M. H.	42	Left, 4.25×4.25 ×2.5 cm.	Moder- ate	Adenopathy	B	6/28/29, radical mastectomy	Wound infected	6/5/29, 2 high voltage treatments	160	23 days	7/21/30, small recurrent lump in the left axilla	Tumor, 2×2 cm.	Infiltrating tubular adenocarcinoma; consid- erable hydropic degenera- tion; axillary nodes free from cancer
E. B.	61	Right, 4×2.5× 2 cm.	Rapid	Adenopathy	B	12/19/27, 3/6/28, 10/24/28, high voltage treatments	100 Cannot be 100 be 70 added	2 mo.	2/2/29, died	

* Axillae also received roentgen treatments.

† The clinical diagnosis was carcinoma because of the adherence to the skin, the firmness, the retraction of the nipple and the axillary adenopathy.

TABLE 8.—Patients with Primary Operable Carcinoma of the Breast Treated by Radium Element Pack

Patient Age	Location of Tumor. Size	Rate of Growth	Axilla* Ade-nopathy	Clinical Index of Malignancy	Operation	Healing of Wound	Radium Element Pack Treatments	Tissue Interval Dosage in Between Breast, Irradiation per Cent, and Skin Operation	End-Result	Gross Pathologic Anatomy	Pathologic Histology
M. T. 62	Left. 12×9×7 cm.	Rapid	Ade-nopathy	B+	10/4/29, radical mastectomy	Primary healing	8/25/29, 30,000 mg. hr. at 10 cm.	40 in 12 days	Metastasis to the liver	Soft hemorrhagic tumor	Infiltrating duct carcinoma; hyalinization of stroma; swelling, hydrops and atrophy of tumor cells; axillary nodes carcinomatous
M. S. 67	Right, 6×5 cm.	Mod-erate	0	A	10/1/29, radical mastectomy	Not good in axilla	9/6/29, 16,000 mg. hr. at 6 cm.	40 in 4 days	No evidence	Soft nodule in breast	Intraductular and intracystic adenocarcinoma; no apparent effect caused by irradiation
I. S. 43	Left, 4×4 cm.	Mod-erate	0	A+	10/11/29, radical mastectomy	Good healing	9/14/29, 16,000 mg. hr. at 6 cm.	50 in 2 days	No evidence	Tumor, 3×2×2 cm.; slightly necrosed	Infiltrating duct carcinoma, grade 2 radioresistant; hyalinization of stroma; collagen swelling; necrosis of fat; atrophy and hydrops of tumor and acidophilic cells with giant nuclei
M. P. 47	Right, 6.5×5.5 cm.	Mod-erate	Ade-nopathy	B	9/20/29, radical mastectomy	Slough of edges, secondary	7/24/29, 32,000 mg. hr. at 6 cm.	55 in 10 days	No evidence	Carcinoma simplex, grade 2 radioresistant; central radium necrosis due to thrombotic occlusion of vessels; peripheral tumor cells unaltered
R. B. 64	Right, 5×5 cm.	Slow	Ade-nopathy	B-	1/10/30, radical mastectomy	Good healing	7/31/29, 16,000 mg. hr. 10/3/29, 16,000 mg. hr. both at 6 cm.	50†	No evidence	No evidence
B. M. 55	Right, 2 masses, 3×2 cm. and 2×2 cm.	Rapid	Ade-nopathy	C-	No operation pulmonary tuberculosis	7/26/29, 32,000 mg. hr. at 6 cm.; total to two masses	100	No evidence, no palpable lump; radio-sensitive	Complete disappearance after first treatment; radioresistant; later reappearance
A. G. 44	Left, 5×4×3 cm.	Mod-erate	0	A	Operation refused	7/17/29, 32,000 mg. hr.; 2/16/30, 16,000 mg. hr.; both at 6 cm.	105† 65†

* The axilla also received treatment by radium element pack.
† The time interval between treatments.

TABLE 9.—Patients with Primary Operable Carcinoma of the Breast Treated by Interstitial Irradiation

Patient and Age	Location of Tumor, Size	Rate of Growth	Axilla	Clinical Index of Malignancy	Operation	Healing of Wound	Interstitial, Milli-curies	Tissue Dosage in Breast, Irradiation, Ery. Skin		Interval Between Irradiation and Operation	Gross Pathologic Anatomy	Pathologic Histology	
								Gold Seeds	Axillary Irradiation, Dose				
L. F. 40	Right, 4×4×3.5 cm.	Mod- erate	Adenopathy	B+	5/29/30, radical mastectomy	Primary healing	4/23/30, 29.3	12	1,000	0*	5 wk.	Hemorrhage and necrosis in tumor, 2×2×2 cm.	Complete destruction of carcinoma in the breast; one axillary node contained cellular adenocarcinoma
B. K. 60	Left, 3×2×2 cm.	Rapid	0	A	6/13/30, radical mastectomy	Axilla healed slowly	5/21/30, 20	8	1,000	0	3 wk.	Necrotic tumor, 2 cm. in diameter	Infiltrating comedocarcinoma; myxomatoid degeneration; marked changes caused by irradiation; questionable viability
L. H. 50	Right, 6×5.5×4 cm.	Mod- erate	Adenopathy	B	10/3/30, radical mastectomy	Primary healing	7/11/30, 64.5	23	1,200	20 mc. in 7 seedst	12 wk.	Hemorrhagic, necrotic tumor, 3×3×2 cm.	Complete destruction of tumor in the breast; hydropic small celled tubular carcinoma in two axillary lymph nodes
A. O. 46	Right, 3.5×3 cm.	Rapid	0	A+	11/15/29, radical mastectomy	Good healing	10/25/29, 32.3	13	1,300	18.9 mc. in 11 seeds	3 wk.	Grayish, irregular, hemorrhagic tumor	Duct carcinoma; complete destruction of the tumor; productive fibrosis; squamous metaplasia of ducts
D. M. 50	Left, 7×6×5 cm.	Slow	0	A	12/20/29, radical mastectomy	Primary healing	10/29/29, 94.65	36	1,350	26.25 mc. in 11 seeds	7 wk.	Fat necrosis; hemorrhage into tumor	Practically complete radium necrosis; atrophy and hydrops of tumor cells; acute thrombosis; originally a duct carcinoma
M. I. 30	Left, 4×3.5×3 cm.	Rapid	0	B	1/31/30, local mastectomy	Healing by second intention	12/26/29, 44.33	14	1,500	20.7 mc. in 9 seeds	1 mo.	Grossly, no tumor present	Heavily irradiated carcinoma of the breast; almost complete destruction; one small focus of tubular carcinoma of questionable viability
G. L. 43	Left, 5×4×4 cm.	Rapid	0	B	12/13/29, radical mastectomy	Slow healing by second intention	10/29/29, 73.64	24	1,900	30.73 mc. in 13 seeds	6 wk.	Tumor, 2.5×2.5 cm.	Infiltrating carcinoma; advanced radium necrosis of tumor; productive fibrosis surrounding regressing non-viable tumor cells; squamous metaplasia of ducts
M. P. 49	Left, 6.5×5×3 cm.	Rapid	0	B	6/26/30, radical mastectomy	Secondary healing	3/4/30, 133	40	2,070	0	3½ mo.	Necrotic shrunken tumor, 2×1.5×1.5 cm.	Carcinoma simplex; total radium necrosis

* Insufficient irradiation.

† No axillary irradiation.

TABLE 10.—Patient with Primary Operable Carcinoma of the

Patient and Age	Location of Tumor; Size	Rate of Growth	Axilla	Clinical Index of Malignancy	Operation	Healing of Wound	Roentgen Treatment	Interstitial, Milli-curies	Irradiation, Gold Seeds	Tissue Dosage in Breast, per Cent, Skin Erythema Doses		
										X-Rays	Interstitial	Total
E. S. 51	Right, 3×3 cm.	Slow	Adenopathy	B—	7/12/29, radical mastectomy	Fair; two small sloughs	6/5/29, 2 high voltage treatments	6/7/29, 12-13	5	160	600	760 in 5 days
J. H. 77	Left, 8×7×3 cm.	Rapid	0	B	1/29/30, 2 high voltage, 1 low voltage treatments	4/16/30, 44.5 (as 2 spheres)	24	135	765	Can not add
B. H. 68	Right, 4.25×4 cm.	Moderate	Adenopathy	B	7/11/29, 3 high voltage treatments	7/20/29, 25	10	180	730	910 in 16 days
E. F. 58	Left, 7×3×2 cm.	Moderate	Adenopathy	B	10/2/29, biopsy	12/3/29, 3 high voltage treatments	11/2/29, 33.3 (as 2 spheres)	18	150	800	950 in 28 days
M. Z. 38	Right, 6×6×4 cm.	Rapid	Adenopathy	B+	10/18/29, radical mastectomy	Primary healing	9/16/29, 2 high voltage treatments	9/21/29, 49.4	14	120	900	1,020 in 18 days
M. B. 50	Left, 5.5×5 cm.	Rapid	Adenopathy	C—	4/25/30, radical mastectomy	Good healing	3/25/30, 3 high voltage treatments	3/18/30, 43	23	150	900	1,030 in 7 days
C. B. 75	Right, 3.5×3 cm.	Slow	Adenopathy	B—	1/29/30, biopsy	Good	1/29/30, 1 high voltage, 2 low voltage treatments	1/29/30, 25	8	160	1,050	1,210 in 9 days
A. M. 61	Right, 3.5×2.5×2 cm.	Moderate	Adenopathy	B	2/11/30, radical mastectomy	Good	12/20/29, 3 high voltage treatments	12/10/29, 29.95	20	125	1,250	1,375 in 10 days
F. V. 64	Left, 4×3.5×3 cm.	Moderate	Adenopathy	B	2/12/30, biopsy	1/31/30, 3 low voltage treatments	2/12/30, 46	18	50	1,565	1,615 in 16 days
C. W. 63	Right, 3×2.5 cm.	Moderate	Adenopathy	B	2/12/30, radical mastectomy	Primary healing	11/21/29, 3 high voltage, 1 low voltage treatments	12/6/29, 30.89	16	125	1,500	1,625 in 25 days
C. S. 67	Left, 6×4.5×2.5 cm.	Rapid	0	B	1/29/30, biopsy	1/28/30, 3 high voltage treatments	1/29/30, 108	36	130	1,800	1,930 in 8 days
M. M. 54	Left, 5×4×3 cm.	Moderate	0	A	8/13/30, radical mastectomy	Secondary healing, dermatitis	12/24/29, 3 high voltage treatments	12/31/29, 74.56	21	100	1,850	1,950
H. S. 72	Left, 3.5×3×1.5 cm.	Moderate	Adenopathy	B	4/9/30, simple mastectomy	Primary healing	1/22/30, 2 high voltage treatments	1/28/30, 46	14	160	1,900	2,060 in 9 days
R. C. 50	Left, 6×6×3 cm.	Moderate	0	A	4/10/30, radical mastectomy	Primary healing	2/24/30, 2 low voltage, 1 high voltage treatments	2/25/30, 111	50	100	2,300	2,400 in 8 days

Breast Treated by Roentgen Rays and Interstitial Irradiation

Axillary Irradiation	Interval Between Irradiation and Operation	End-Results	Gross Pathologic Anatomy	Pathologic Histology
X-rays	5 wk.	No evidence	Tumor, 1×1 cm.	Infiltrating carcinoma simplex, grade 2 radioresistant; vacuolated hydropic viable tumor cells; fibrosis, slough and partial destruction; sublethal dose
X-rays	Regressing	
X-rays	8/12/29, only ¼ former size; 12/6/29, death from cardiac failure	
X-rays	Only slight regression; radioresistant	Intracystic or intraductular adenocarcinoma
X-rays	No evidence	Tumor, 3×3×2 cm.; hemorrhage and necrosis	Infiltrating duct carcinoma; marked changes, in places total destruction; productive fibrosis; squamous metaplasia
X-rays plus 26 mc. in gold seeds	1 mo.	Good to date	Tumor, 5×3×2 cm.; numerous portions necrotic and hemorrhagic	Infiltrating duct carcinoma, grade 2 radioresistant; radium effect focal, leaving some viable carcinoma; axillary nodes are carcinomatous
X-rays	Small cell infiltrating carcinoma; calcification; vascular changes; radiation changes after x-ray therapy
X-rays	7 wk.	Good to date	Tumor, 3×3×1 cm.	Tubular carcinoma of ducts; radioresistant; sclerosis and calcification of vessels; collagen swelling; atrophy and hydrops of tumor cells; productive fibrosis
X-rays plus 27 mc. in 10 gold seeds	Good to date—regression	Two weeks after x-ray therapy, fibrocarcinoma of ducts; radioresistant
X-rays plus 31 mc. in 14 gold seeds	2 mo.	No evidence	Fibrotic mass, 2 cm.	Complete destruction of carcinoma in breast; one node contained atrophied carcinoma
X-rays	No evidence of tumor; no loss of skin	Biopsy before interstitial irradiation; small cell fibrocarcinoma with advanced radiation changes, particularly vascular
X-rays plus 30 mc. in 10 gold seeds	8½ mo.	Excoriation; tumor gone; fibrosis	No residual cancer; evidences of heavy irradiation
16 mc. in 5 gold seeds	10 wk.	No evidence		Biopsy, infiltrating carcinoma; amputated specimen; no evidence of carcinoma
X-rays	6 wk.	Tumor, 3.5×2.5 cm.; myxomatous stroma	Total destruction of all tissues; squamous metaplasia of ducts; small regressing nonviable focus in an area of abortive fibrosis

TABLE 11.—*Patients with Primary Operable Carcinoma of the Breast*

Patient and Age	Location of Tumor, Size	Rate of Growth	Axilla	Clinical Index of Malignancy	Operation	Healing of Wound	Radium Element Pack Treatments	Interstitial, Millicuries	Irradiation, Gold Seeds
C. W. 39	Left, 7×6.5 cm.	Moderate	Adenopathy	B+	10/11/29, radical mastectomy	Secondary healing	8/29/29, 16,000 mg. hr. at 6 cm.	9/12/29, 40.75	13
T. A. 42	Right, 6×4.5×3 cm.	Slow	0	A	9/25/29, radical mastectomy	Secondary healing, necrosis of the edge of the skin	8/12/29, 16,000 mg. hr. at 6 cm.	8/20/29, 33	18
E. S. 53	Right, 8×8×7 cm.	Moderate	Adenopathy	B	Refused	9/12/29, 16,000 mg. hr. at 6 cm.	10/10/29, 77.64	29
N. J. 54	Right, 2.5×2.5 cm.	Moderate	0	A	11/29/29, radical mastectomy	Secondary healing, slight necrosis	8/25/29, 16,000 mg. hr. at 6 cm.; 8/23/29, tray 3,000 mc. hr. at 3 cm.	8/28/29, 12.3	5
E. P. 46	Left, 5.5×3 cm.	Slow	0	B	8/20/29, radical mastectomy	Primary healing	6/1/29, 16,000 mg. hr. at 6 cm.	7/10/29, 41.15	18
F. S. 66	Right, 6×4.75 cm.	Moderate	0	A	1/8/30, local mastectomy	Primary healing	6/4/29, 32,000 mg. hr. at 6 cm.; two areas	7/9/29, 48	22
H. W. 40	Right, 7.5×7 cm.	Rapid	Adenopathy	C	9/20/29, 16,000 mg. hr. at 6 cm.	10/15/29, 85.7	24
E. K. 69	Right, 5.5×3 cm.	Moderate	Adenopathy	B	9/19/29, biopsy	8/23/29, 16,000 mg. hr. at 6 cm.	9/21/29, 50.7	18
M. F. 66	Right, 7×6.5 cm.	Rapid	Adenopathy	B+	2/7/30, radical mastectomy	Seven weeks to heal by secondary intention	10/26/29, 24,000 mg. hr. at 6 cm.	1/17/30, 86	30
E. G. 47	Right, 4.5×4×2 cm.	Moderate	0	B	10/11/29, radical mastectomy	Good healing	8/13/29, 24,000 mg. hr. at 6 cm.	8/31/29, 40	13
M. S. 66	Right, 3.5×3.5 cm.	Moderate	0	A	None, cardiac complications	9/7/29, 16,000 mg. hr. at 6 cm.	9/27/29, 30.36	13
L. E. 62	Right, 6×6×5 cm.	Rapid	Adenopathy	B+	None, diabetic complications	9/11/29, 16,000 mg. hr. at 6 cm.	9/28/29, 72.3	19

Treated by Radium Element Pack and Interstitial Irradiation

Tissue Dosage in Breast, per Cent, Skin Erythema Doses			Interval Between Irradia- tion and Opera- tion	End-Results	Gross Pathologic Anatomy	Pathologic Histology	
Radium Element Pack	Inter- stitial	Total					
50	585	635 in 17 days	Radium element pack	1 mo.	No evidence	Softening of tumor	Comedocarcinoma, partly intra- ductular; tumor cells are atrophic, hydropic and eosinophilic; vessels thrombosed and recanalized
50	600	650 in 9 days	Radium element pack	5 wk.	No evidence	Tumor, 1×1 cm.; fat necrosis; only one small nodule	Infiltrating carcinoma; radiation changes in stroma cells of tumor are markedly atrophic, hydropic and vacuolated
35	865	900 in 30 days	Radium element pack plus 29 mc. in 11 gold seeds	Tumor mass fibrotic, 3.5× 3 cm.; skin intact		
100	800	900 in 4 days	0	3 mo.	No evidence	Major portion of carcinoma com- pletely destroyed; few nonviable tumor cells in abortive fibrosis
40	900	940 in 40 days	Radium element pack plus 700 mc. hr. with radium needles	5½ wk.	No evidence	Tumor, 4×2 cm.; half of tumor necrotic	Cellular carcinoma; too necrotic to classify; nonviable cells; only shadow cells; squamous metaplasia of ducts
70	880	950 in 30 days	Radium element pack plus 22 mc. in gold seeds	6 mo.	No evidence; cancer of the tongue	Tumor, 2.5× 2.5 cm.; cir- cumscripted	Adenocarcinoma, partially gelatin- ous; mainly distributed in a peripheral narrow zone about a wide area of radiation fibrosis
45	1,050	1,095 in 38 days	Radium element pack plus 25 mc. in gold seeds	Tumor entirely disappeared in the breast and axilla; metas- tases to the lung		
50	1,100	1,150 in 30 days	Radium element pack	Complete dis- appearance of tumor	Infiltrating scirrhus carcinoma on biopsy
50	1,200	Cannot be added	Radium element pack plus 30 mc. in gold seeds	3 wk.	No evidence; radio- sensitive	Tumor clini- cally disap- peared after external irradiation	Complete destruction of carcinoma of the breast; one small focus of regressing cells in abortive fibrosis; metaplastic cartilage and bone
90	1,175	1,265 in 19 days	Radium element pack	6 wk.	No evidence	Tumor, 3×2.5 cm.; hemor- rhage about tumor	Infiltrating carcinoma; partial total destruction; atrophic regressing tumor cells in one area of abortive fibrosis; mucoid changes
60	1,250	1,310 in 23 days	Radium element pack plus 15.6 mc. in 7 gold seeds	2/3/30, only scar in breast	
50	1,330	1,380 in 18 days	Radium element pack plus 21 mc. in 7 gold seeds	Tumor of the breast gone; new node in right axilla	

On the other hand, a great dosage within certain limits is not incompatible with good wound healing providing the important interval of time between irradiation and operation is maintained.

Case 10, table 10, 1,625 per cent S. E. D. Interval of 42 days.

Case 7, table 9, 1,800 per cent S. E. D. Interval of 68 days.

Case 13, table 10, 2,060 per cent S. E. D. Interval of 70 days.

Case 14, table 10, 2,400 per cent S. E. D. (111 millicuries). Interval of 42 days.

Postoperative External Irradiation.—In the present series of primary operable carcinomas of the breast, we have purposely withheld all postoperative external irradiation in order to evaluate correctly the end-results of preoperative irradiation in measured tissue doses. Prior to these experiments, a routine cycle of roentgen irradiation was given three or four weeks following the operation. By this time the wound had healed, and the patient had recovered sufficiently to undergo treatment without much distress. In our hands, the results have been better when postoperative irradiation has followed surgical intervention than when operation alone has been employed. In general, surgeons have been more willing to submit their patients to postoperative irradiation than to preoperative treatment, in the belief that the likelihood of local recurrence in the operative field was thereby diminished. A continuous follow-up on these patients, month by month, may reveal evidences of recurrence, to which appropriate treatment may be applied. Sufficient data are at hand to prove that postoperative irradiation diminishes the liability to recurrence and prolongs considerably the life of the patient. Yet there are three possible arguments against the procedure: the dosage delivered is insufficient to destroy any viable carcinoma left in the operative field, although it may be instrumental in inhibiting the growth of such cells by enveloping them in dense scar tissue; if a recurrence does appear after irradiation, the intensity of the subsequent treatments must be lessened because of the diminished tolerance of the skin, and carcinomas that have recurred in the face of irradiation probably have an increased radioresistance. The postoperative roentgen treatments are usually given twice a week, with exposure of the same areas used in the preoperative cycle. The dose employed for the supraclavicular and axillary spaces is relatively somewhat heavier than that over the anterior thoracic wall. The breast having been removed, only a superficial dose is necessary over the anterior wall of the chest, whereas for the axilla and supraclavicular regions, a relatively greater depth dose seems indicated. For this reason, high voltage roentgen treatment is given to the axilla and supraclavicular space, and low voltage roentgen treatment to the mammary site on the anterior thoracic wall.

THE PATHOLOGIC CHANGES PRODUCED BY IRRADIATION IN CARCINOMA OF THE BREAST

It is perhaps unfortunate that conclusions on the mechanism of the changes produced by radiation must be derived from a rather heterogeneous material. We have not had a sufficiently large group of cases treated by any one method to enable us to draw conclusions regarding the precise effect of the particular mode of treatment. Patients differ in age and physical status. Carcinoma of the breast is not one disease but a group of diseases, differing in gross anatomy, pathologic histology, radiosensitivity and clinical course. One cannot, for example, compare bulky adenocarcinoma with diffusely infiltrating multiple foci of duct carcinoma. Again, some duct carcinomas are made up of large cells, so large and flattened that they resemble the cells of squamous carcinoma. Others infiltrate widely in small strands of small cells or form masses made up of cells that on superficial examination might be considered lymphosarcoma. Although there are no precise observations on the radiosensitivity of differing types of cancer of the breast, no one who has studied the question of the radiosensitivity of tumors in general can doubt that great differences must exist in the field of carcinoma of the breast. In a group of patients, some treated by roentgen rays alone, some by radium element pack, some by roentgen rays and element pack, some by roentgen rays or radium element pack, or both, combined with interstitial radium emanation, and others by buried emanation alone, with all the varying dosage and time factors, we are far from having a satisfactory experiment even in human biology.

Like all tumors, carcinoma of the breast is subject to many spontaneous changes. Bulky tumors become infarcted; ulceration and infection produce marked changes; thrombosis and obliterative arteritis are spontaneous occurrences; hyaline swelling of the stroma is rather common and, rarely, calcific deposits are found. In other words, many of the changes found to a marked degree in the irradiated tumor of the breast occur to a lesser extent in the untreated or moderately treated case. Therefore, in our cases that have received but small doses by external irradiation one must make a nice distinction between what one regards as the effect of the treatment and the possible spontaneous degenerative processes within the tumors.

Histologic studies seem to indicate that radiation affects tumors (1) by direct influence on the tumor cell and (2) through vascular changes, arteritis, thrombosis or slow vessel occlusion and productive fibrosis. In certain tumors, the direct effect seems most prominent, in others, the second factor. The two modes of action are by no means exclusive, and at the present time no one can say what this so-called direct effect

on the tumor cells is, in what manner it is dependent on alteration of intracellular electrolytes, changes in permeability and the like. The tendency is to assume a direct effect on the tumor cell in tumors in which examination fails to reveal sufficient accessory tissue alterations to account for the disappearance of the disease.

If one were to attempt an estimation of the radiosensitivity of carcinomas of the breast, one might list them in the order of increasing sensitivity somewhat as follows, acknowledging, however, that sufficient observations in the radiosensitivity of carcinoma of the breast are not

TABLE 12.—*Patients with Primary Operable Carcinoma of the Breast Treated by*

Patient 'and Age	Location of Tumor, Size	Rate of Growth	Axilla	Clinical Index of Malignancy	Operation	Healing of Wound	Roentgen Treat- ments	Radium Element Pack Treat- ments	Inter- stitial Milli- curies	Irra- dia- tion, Gold Seeds
K. S. 65	Left, 5×4.5 cm.	Rapid	Ade- nopathy	B+	0	2/8/28, 2 high voltage treat- ments	2/13/28, 8,000 mg. hr. at 6 cm.
M. C. 49	Right, 6×5.5 cm.	Slow	Ade- nopathy	B—	12/20/28, radical mas- tectomy	Good healing	2/24/28, 2 high voltage treat- ments	3/7/28, 16,000 mg. hr. at 6 cm.
H. N. 79	Left, 5×4.5 cm.	Slow	Ade- nopathy	B—	0, age	6/25/29, 3 high voltage treat- ments	8/8/29, 16,000 mg. hr. at 6 cm.	8/17/29, 22.4	10
B. H. 34	Right, 8×5× 3.5 cm.	Rapid	Ade- nopathy	C	11/20/29, radical mas- tectomy	Incomplete closure graft	5/20/29, 3 high voltage treat- ments	6/10/29, 32,000 mg. hr. at 6 cm. over two areas	10/17/29, 89.1	22

available: (1) sclerosing fibrocarcinoma, (2) large cell infiltrating duct carcinoma (carcinoma simplex), (3) small cell infiltrating duct carcinoma (carcinoma simplex), (4) solid medullary carcinoma, (5) intraductular comedocarcinoma, (6) intracystic adenocarcinoma, and (7) certain very small cell carcinomas superficially resembling lymphosarcomas.

Increasing anaplasia within the individual groups increases the sensitivity. Ewing has said: "Carcinomas are resistant in inverse proportion to the degree of anaplasia and in direct proportion to the amount of desmoplastic reaction which they excite." Sensitivity is altered by the clinical setting. Anemia and cachexia decrease sensitivity; inflammatory characteristics (acute inflammatory carcinosis) increase it. The gelatinous character of the colloid carcinomas of the breast prevents an adequate reaction of the tissues to irradiation. The large intracystic

adenocarcinomas owe their radiosensitivity to their rapid growth, especially to their unstable vascularity, which accounts for the frequent bulky necrosis of these tumors following irradiation. In other words, we are dealing with a complex problem, with facts difficult of statement and ascertainable only by experience.

Radiosensitivity is in no sense an exact criterion of the ultimate ease of cure (even though local cures are affected), because these more cellular tumors usually metastasize more readily and widely. The well known law of Bergonie and Tribondeau established the definite relation-

Combinations of Roentgen Rays, Radium Element Pack and Interstitial Irradiation

Tissue Dosage in Breast, per Cent, Skin Erythema Doses				Interval Between Irradia- tion and Opera- tion	End-Results	Gross Pathologic Anatomy	Pathologic Histology
X-Rays	Radium Element Pack	Inter- stitial	Total				
110	30	...	140 in 15 days	Axillary Irradiation X-rays	11/28, died	
125	60	...	185 in 12 days	X-rays	9 mo.	3/30, tumor of the breast was 2 cm. in diam- eter; 11/30, no tumor present	Necrotic tumor mass, 4.5×3 cm. Adenosarcoma; degenerated; hemorrhage; metastases to lymph node were car- cinomatous
140	50	550	740 in 2 mo.	X-rays plus radium ele- ment pack plus 15 mc. in gold seeds			
80	70	1,000	Cannot be added	X-rays plus 24.5 mc. in gold seeds	6 wk.	Softened tumor; calcifi- cation; hemor- rhage in tumor Infiltrating comedocarci- noma; hyaline stroma; productive fibrosis; squamous metaplasia of ducts; marked swellings and degeneration of tumor cells

ship of the grade of malignancy to the degree of radiosensitivity. Moreover, some mammary cancers have periods of apparent latency with later resumption of activity; the radiosensitivity of such a cancer fluctuates with its growth proclivities. Our experiment has been based on the assumption that true radiosensitivity is proportional to the spatial dose of rays absorbed necessary to sterilize the cancer. We possess no method of estimating the dose of rays actually absorbed by the cells of any tumor, but we can determine with some degree of accuracy the amount of irradiation delivered to the cells of the tumor necessary to effect their destruction.

The nature of the tumor bed is an important factor in radiation therapy for carcinoma of the breast, because the fatty envelope retards the response to treatment. This fact alone accounts for the seeming

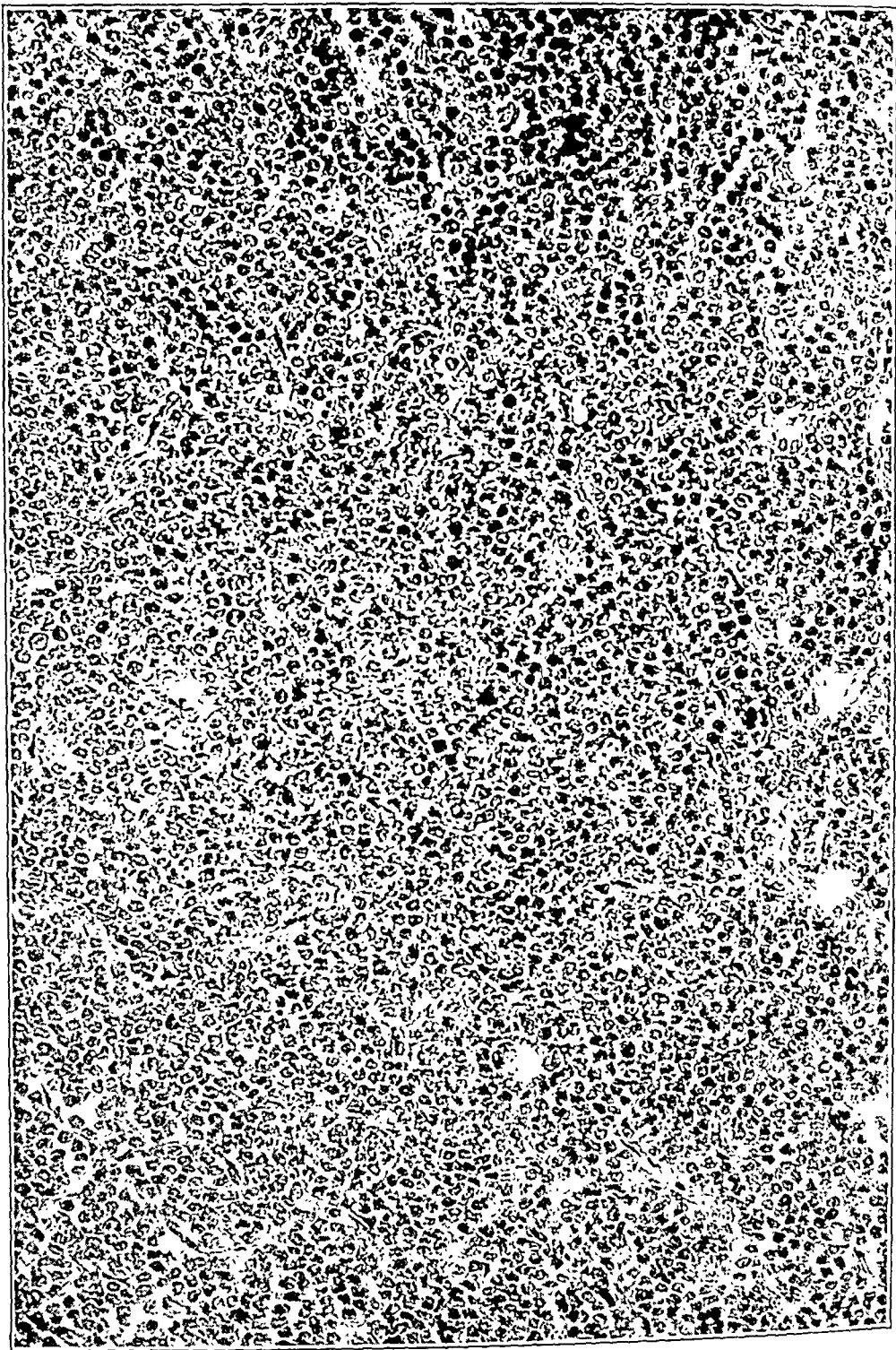


Fig. 13.—Area of diffuse small cell carcinoma; the cells resemble those of lymphosarcoma; other areas in this tumor, more radioresistant, showed tubular and alveolar carcinoma, grade 4; marked radiosensitivity; rare type.

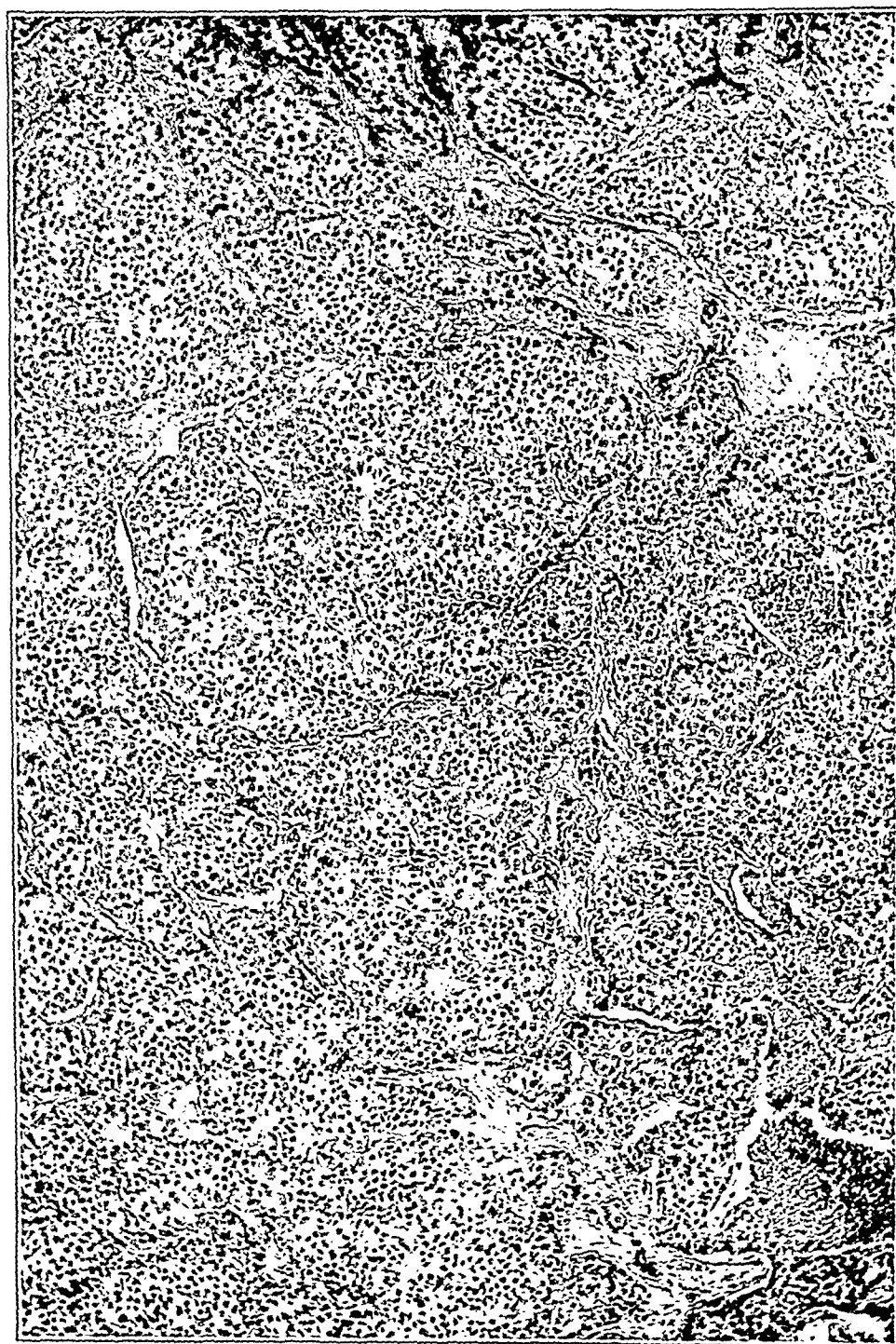


Fig. 14.—Solid alveolar duct carcinoma. The cells were relatively large. Radioresistant; grade 2.



Fig. 15.—Small cell infiltrating duct carcinoma, grade 3. Other areas of this tumor showed a diffuse growth resembling lymphosarcoma. Relatively radio-resistant type.

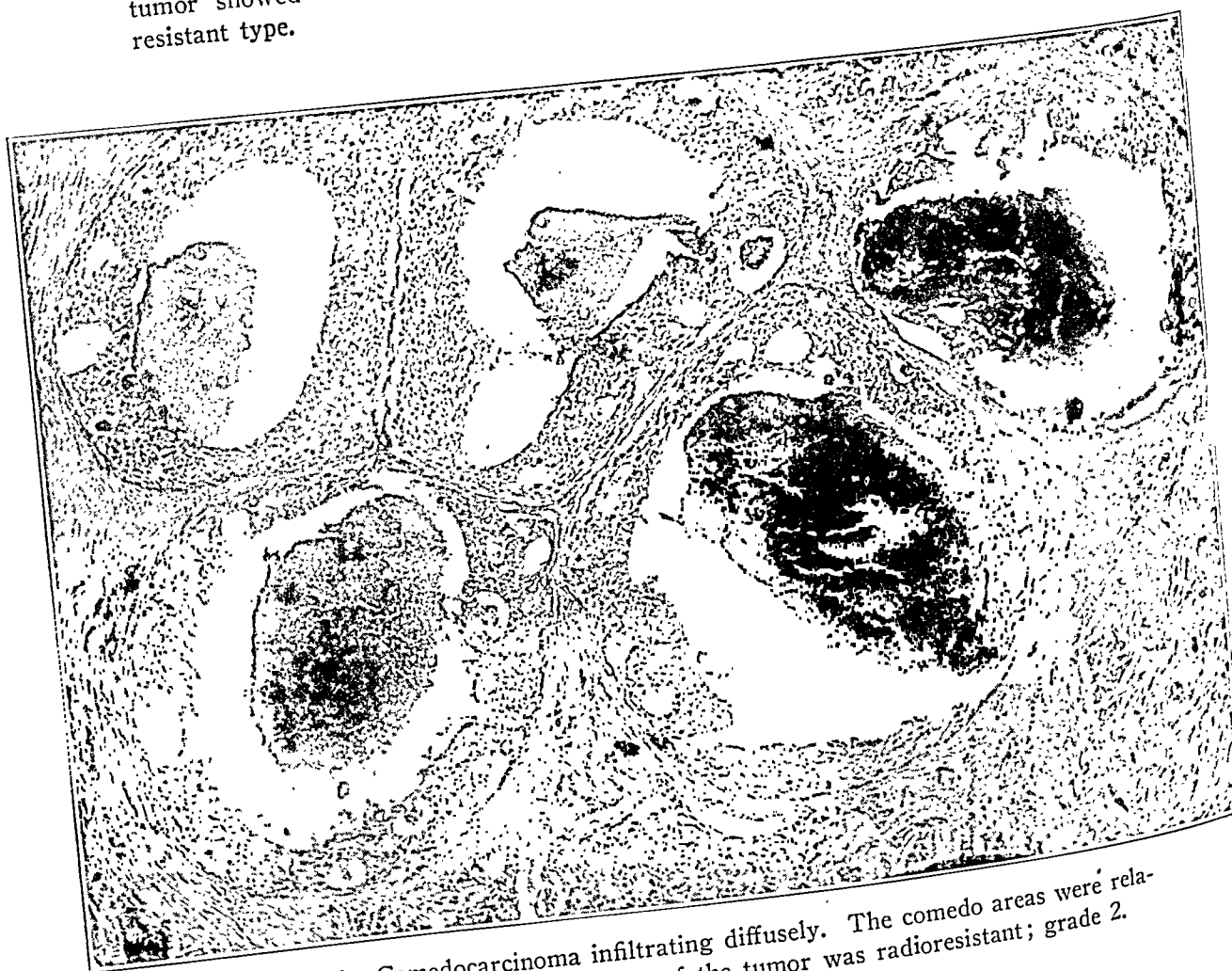


Fig. 16.—Comedocarcinoma infiltrating diffusely. The comedo areas were relatively radiosensitive and the balance of the tumor was radioresistant; grade 2.



Fig. 17.—Bulky adenocarcinoma (medullary carcinoma) showing a tendency to spontaneous necrosis; blood supply was unstable. Relatively radiosensitive, owing to the readiness with which blood supply was interfered with by irradiation.



Fig. 18.—Intracystic papillary adenoma malignum, relatively radiosensitive on account of papillary structure. Clinically, the lesion was essentially benign.

great radioresistance of many mammary cancers. Ewing has said that, "Fat tissue with the low metabolism of fat deposits is highly resistant to radiation, but after heavy dosage, the cell membranes rupture, minute oil cysts form, saponification occurs, new blood vessels appear, and there is considerable proliferation of the fat cells which are difficult to destroy when invading fat tissue." This fact has stimulated us to use larger and still larger doses of interstitial irradiation in the breast in an attempt to improve the tissue reaction by inducing fat necrosis, the infiltration of

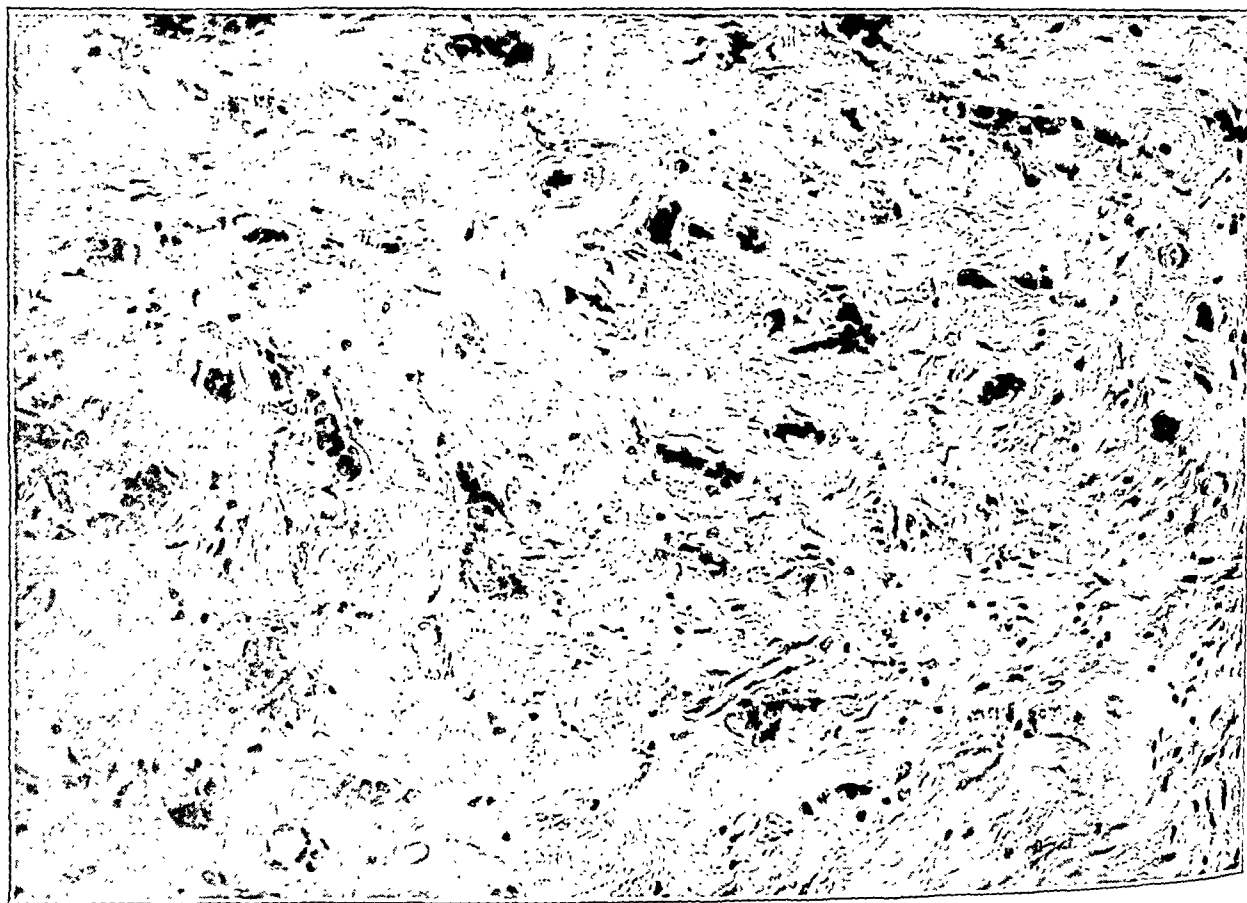


Fig. 19.—Radioresistant fibrocarcinoma (scirrhous), grade 2.

plasma cells and leukocytes, the augmentation of blood supply and the formation of granulation tissue in the neighborhood of the cancer.

Acquired Radioresistance.—It is probable that an immunization of the neoplasm results from the administration of repeated and long-spaced sublethal irradiations. Hence, there is a progressive diminution in radio-sensitivity under the influence of repeated inadequate treatments with radium. Possibly the more radioresistant cells of successive generations are those which persist after these repeated treatments, and thereby are selectively culled from the original tumor after the manner of selective breeding. For very advanced cancers, in which the administration of a

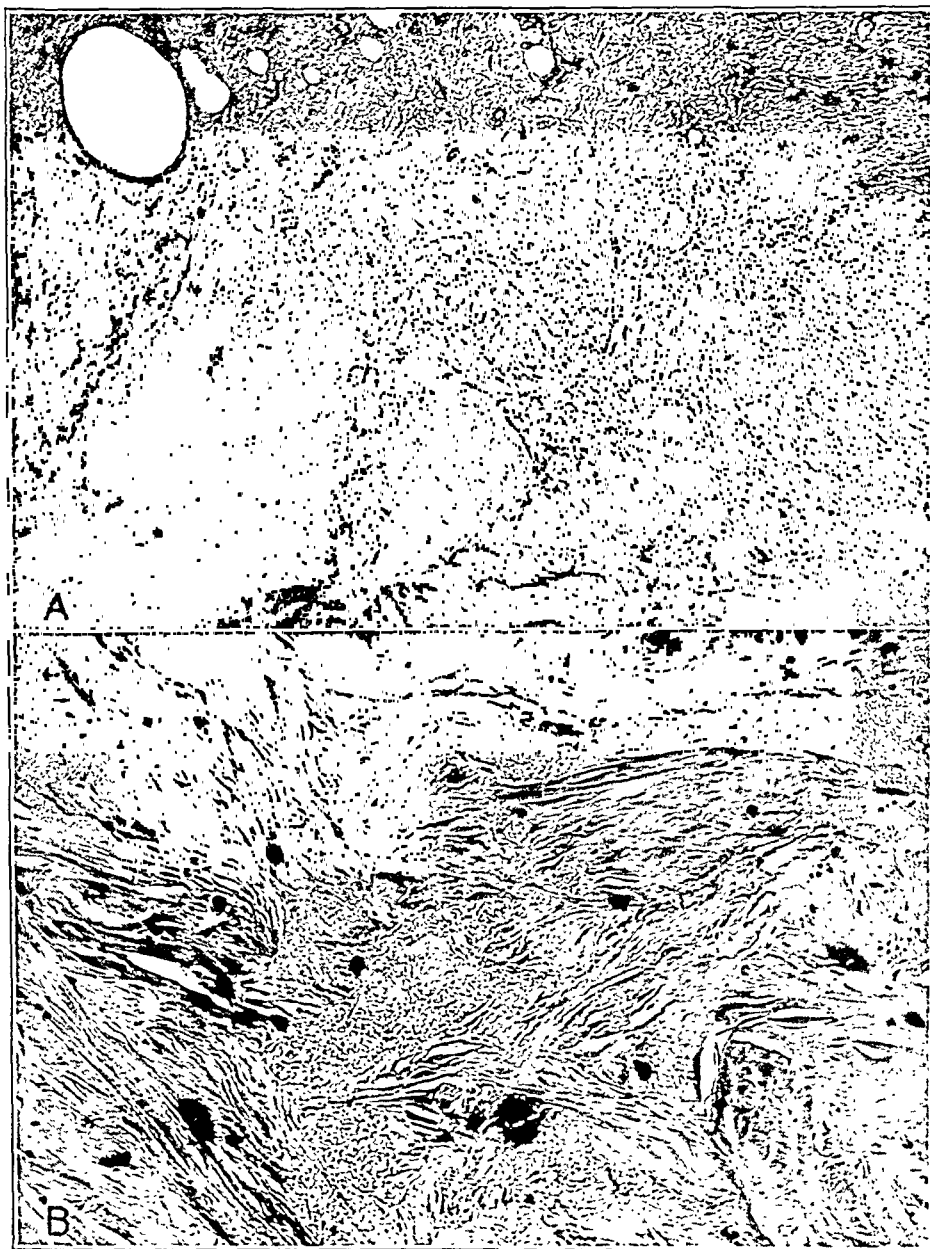


Fig. 20.—*A*, complete necrosis of tumor, showing fibrin, capillary necrosis and inflammation of fat tissue. *B*, fibrosis; foci of calcific deposit at the site of the destroyed tumor cells.



Fig. 21.—*A*, regression of atrophic, hyperchromatic tumor cells in the midst of extreme productive fibrosis. *B*, productive fibrosis, abortive fibrosis and atrophic tumor residua.

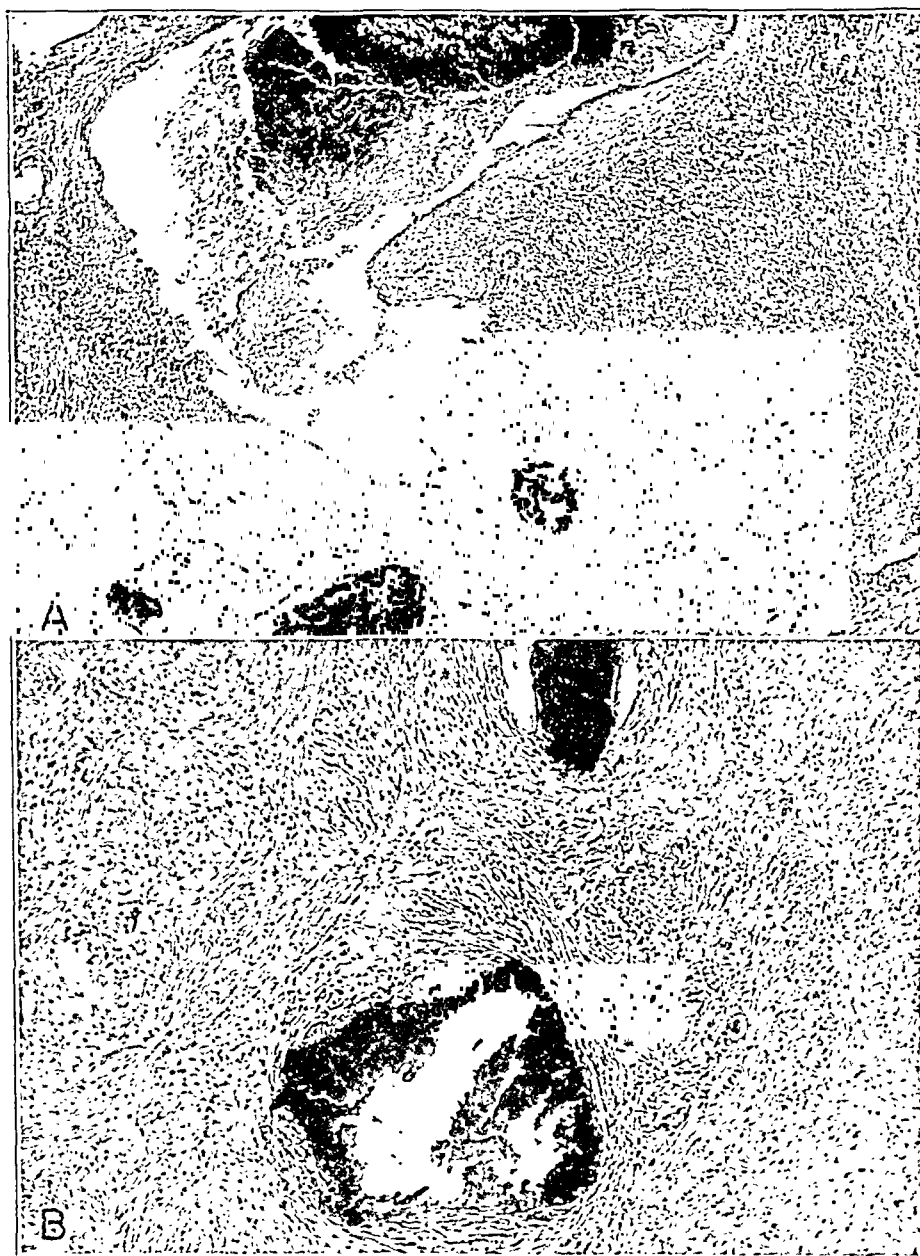


Fig. 22.—*A*, sloughing and calcification in comedocarcinoma, with marked lymphocytic infiltration. *B*, calcific deposits in sloughing comedocarcinoma.

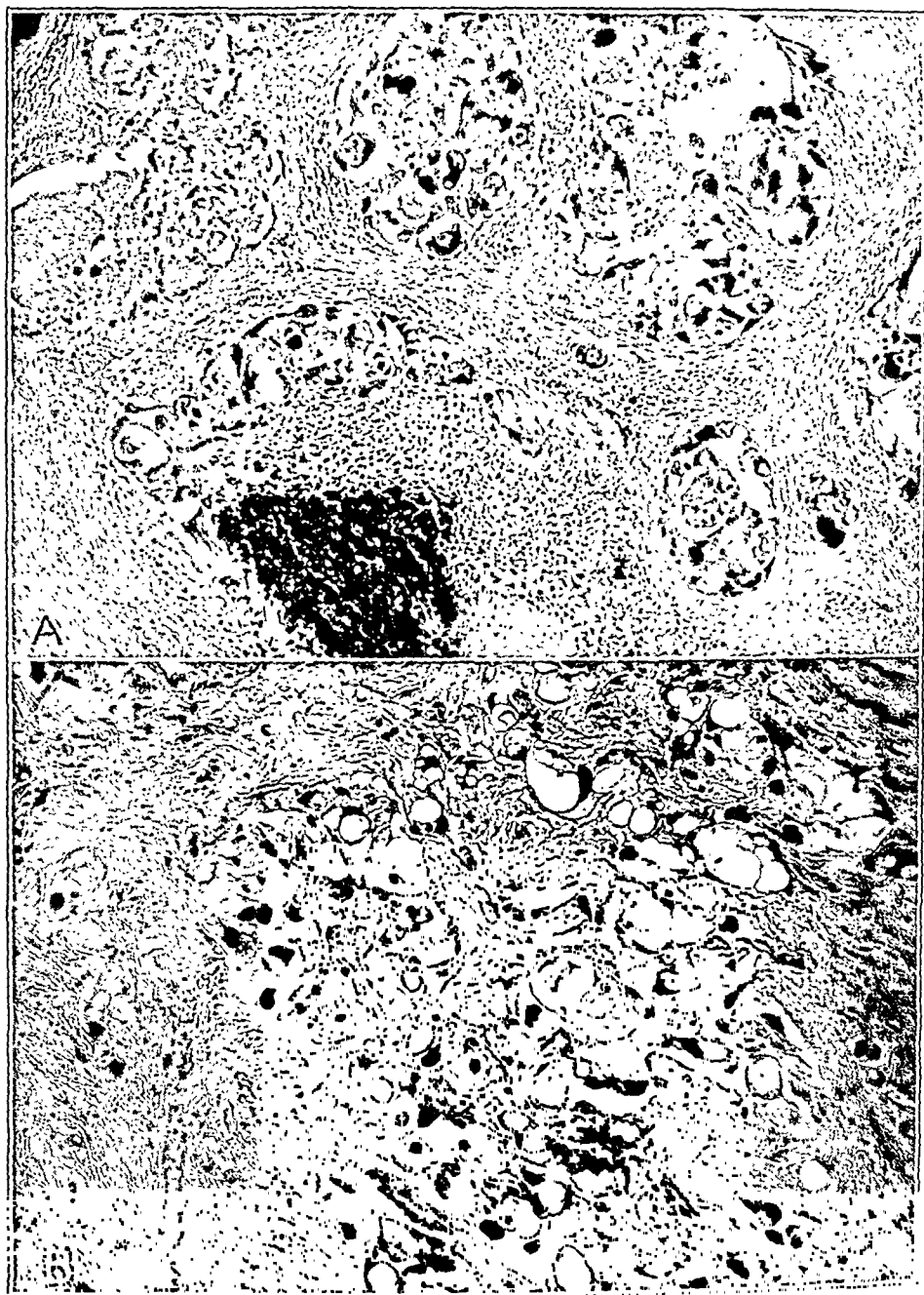


Fig. 23.—*A*, sloughing comedocarcinoma, showing large, hydropic, squamous-like cells, with giant, degenerative nuclei. Earlier stage of calcification in area of hemorrhage, sloughing and accumulation of fatty endothelial leukocytes. *B*, regression of carcinoma, with squamous metaplasia, degenerative hyperchromatism and extreme hydropic changes.



Fig. 24.—*A*, calcific vascular deposit following external irradiation. *B*, squamous metaplasia in normal areas of the breast adjacent to the tumor which had been interstitially irradiated.

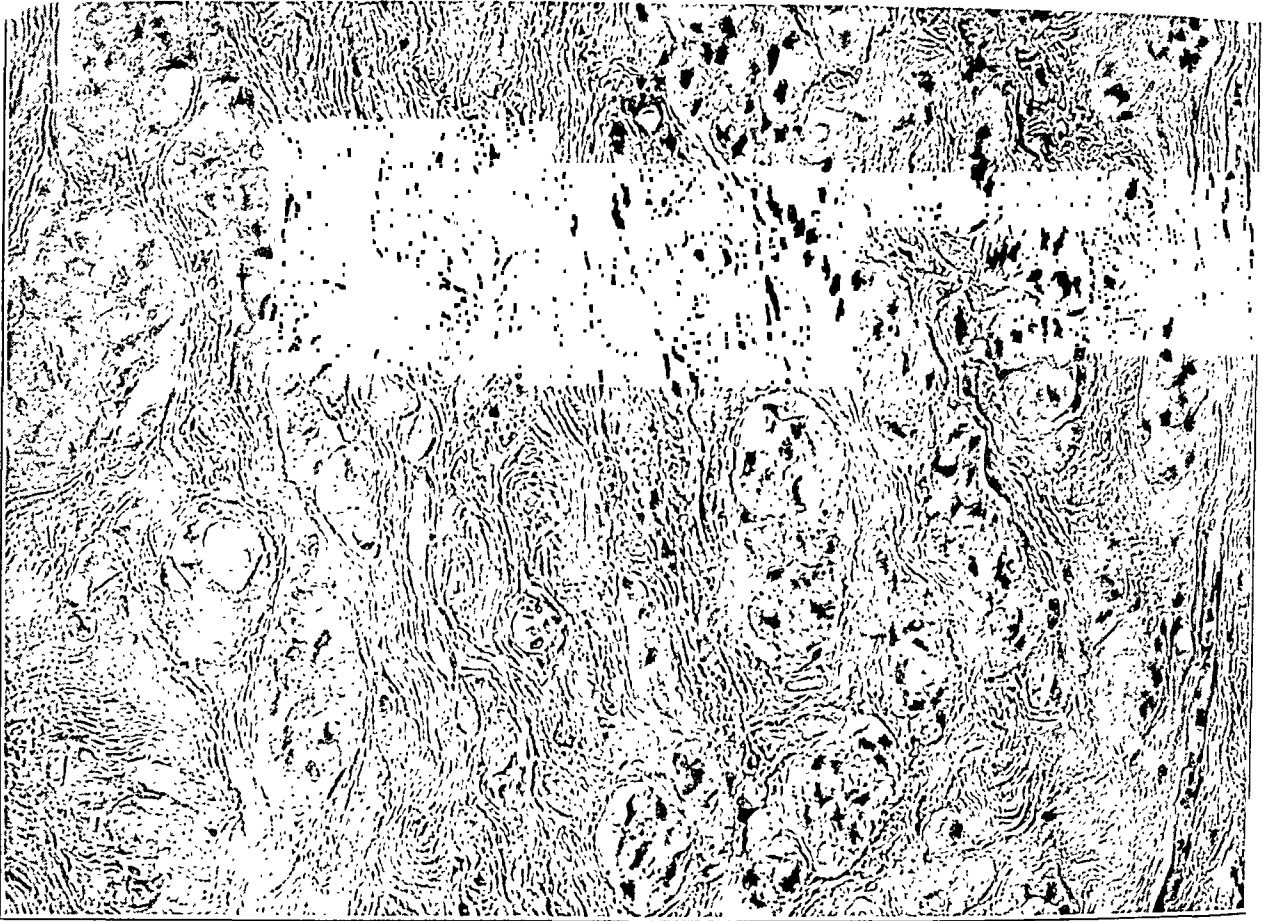


Fig. 25.—Photomicrograph of a mammary cancer that had received 350 per cent of a skin erythema dose of radium. Note the carcinoma cells.

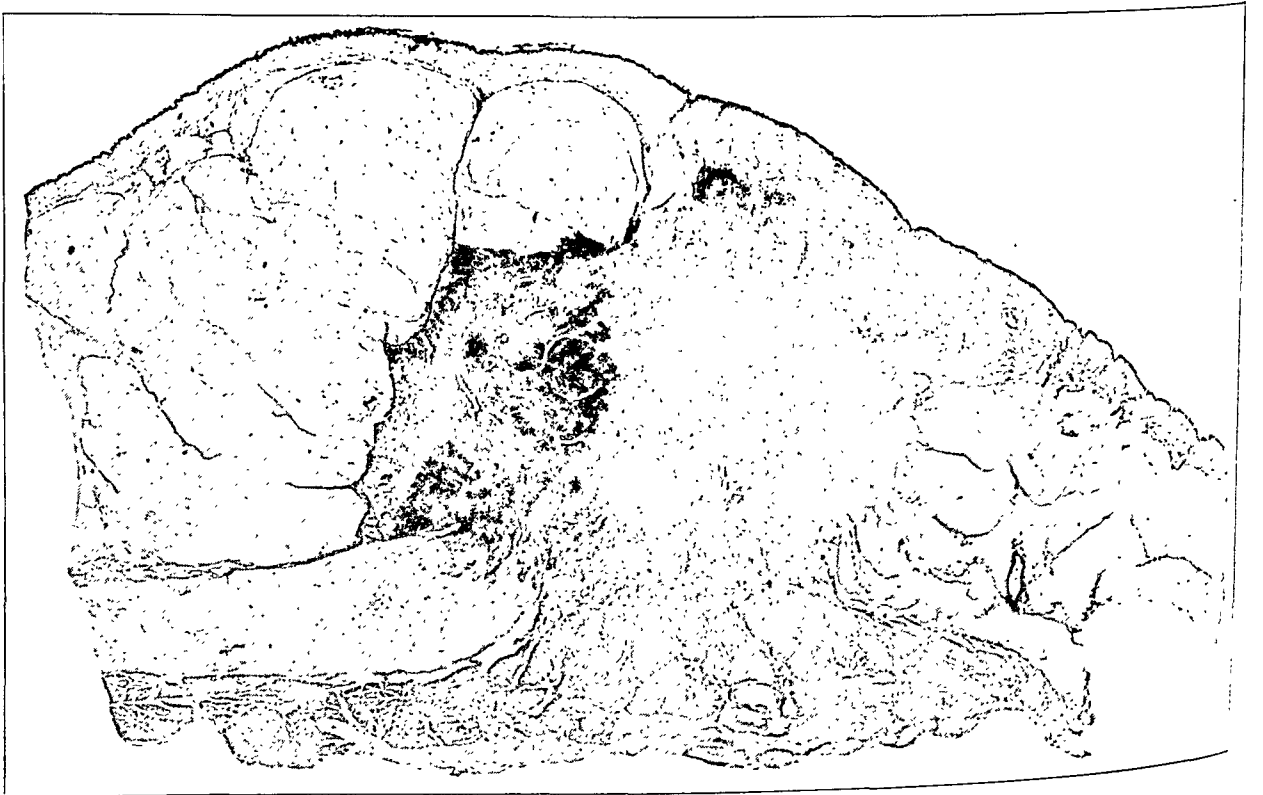


Fig. 26.—Whole section of breast with an untreated bulky adenocarcinoma which involved the skin and the muscle.

large dose of irradiation is dangerous, one may purposely employ fractionation and espacement of doses, which result in only temporary palliation. Radioresistance is not an instantaneously acquired but a latent property of cancer tissue. It is not easily produced by the administration of a small dose of radium; it is not manifested immediately after the administration of a strong dose of irradiation. The radio-immunization may occur after a single intensive treatment or after a series of irradiations with fractionation of the dose. It is after a delay of from six weeks to two months that the phenomenon becomes apparent, and it attains its maximum even later. Once acquired, this radioresistance persists indefinitely. At the same time that the neoplastic tissue is becoming refractory to radium or roentgen rays, the general tissues (connective tissue, blood vessels) are rendered incapable of supporting a new cycle of radium or roentgen treatment without great danger of necrosis. Tumor restraint rather than destruction is obtained in this manner. These dormant cancer cells lying in indolent foci in beds of scar tissue, retain enough vitality to grow again when sufficient provocation occurs. The reappearance of cancer in the irradiated field presents a difficult problem in treatment, owing to this acquired radioresistance. "Abortive fibrosis" is a term that Ewing has applied to a form of indolent fibrosis with destruction of all tissue cells and most blood vessels, but with persistence of tumor cells. Even in the breast, he found wide hyaline strands of fibrous tissue enclosing groups of well preserved tumor cells, which maintain their nutrition through scanty but rigid sinusoid blood vessels. Ewing believed that these tumor cells acquired an increased radioresistance greater than that of the normal tissues, and that this condition results more often after radium than after roentgen treatment. Although the desired attainment in the case of advanced inoperable mammary cancers, the discovery of abortive fibrosis in a breast with a condition classified as primary operable carcinoma is proof of improper or insufficient irradiation.

Changes Produced by Measured Tissue Doses of Irradiation.—In reviewing sections from carcinomas of the breast treated by high voltage roentgen rays or by element pack alone, certain facts seem apparent. In two patients receiving 100 and 110 per cent of skin erythema doses in the tumors, the changes produced were negligible. In the second case, a portion of the tumor had undergone regression and showed local areas of abortive fibrosis resulting from vessel occlusion. There was considerable calcification, but the patient had a slowly growing tumor and was 71 years old. Probably the calcification was a spontaneous change. One hundred and thirty per cent of skin erythema doses of roentgen rays in one patient produced slight atrophy of the tumor cells within one month, and in a second case caused complete regression of a radiosensitive carcinoma—one of the rare, unexplained cases undoubtedly car-

cinoma but of unknown type. Three tumors receiving doses of 140 per cent showed insignificant changes in ten days, some productive fibrosis in three weeks, but considerable atrophy with sloughing and calcification in two months. This might suggest that the effects increase with the interval of time between treatment and amputation, but, unfortunately, we have no basis for conclusions from these three cases, since they comprised three different tumor types: a gelatinous carcinoma, a bulky adenocarcinoma and a moderately small cell duct carcinoma. Two tumors treated with element pack alone disappeared completely. Again, unfortunately, we do not know the type of tumor. Two patients receiving 40 and 50 per cent S. E. D. into the tumor mass, followed by amputation three and four weeks later, showed no significant tissue changes. One patient received 40 per cent, and at amputation five weeks later the tumor cells were swollen and hydropic, or atrophic with the stroma much swollen. A fourth breast receiving 85 per cent and amputated two months later showed swollen, hyalinized stroma, hydrops and atrophy of the tumor cells, many acidophilic tumor cells with degenerative, giant nuclei. A wide focus of necrosis and fibrosis had resulted from vascular occlusion. Although it is difficult to be certain, we gain the impression that the smaller tumor doses from the radium element pack are slightly more effective than larger doses of roentgen ray. Save for the rare, unexplained, total disappearance of tumor masses, it is obvious that the doses deliverable by external radiation alone have been quite inadequate in controlling the disease.

Adequate interstitial radiation, when properly placed, completely alters the anatomy of the tumors. Complete destruction may occur and does occur with the larger doses. The tumors soften, and the lesions assume more nearly the appearance of a fibrous mastitis. Often the tissue is glistening and gelatinous. It may be difficult to tell by palpation where the tumor ends and the fibrous mastitis begins. About the seeds are areas of yellow, opaque, granular, necrotic material often infiltrated with blood. The fatty tissue undergoes necrosis. Bulky adenocarcinomas slough within their capsules. Even when total destruction does not occur within the time elapsing between interstitial radiation and amputation, the tumors shrink markedly. Histologically, the pictures are variable. Some tumors vanish, leaving only wide areas of necrosis with hemorrhage, acute necrosis of vessels, collagen, tumor and fat—shadows of the original disease. The anatomic picture indicates that these are the more cellular adenocarcinomas and medullary carcinomas. The infiltrating duct carcinomas with moderate or large amounts of stroma are more resistant and disappear by progressive atrophy. Their cells are often hydropic and undergo a type of squamous metaplasia preceding necrosis. Swelling occurs in the connective tissue, proliferation may be marked, and the end-result may be abortive fibrosis or minute calcific

masses in the dense hyaline connective tissue. Lymphocytic infiltration may be prominent but may not be attributable to the treatment. Comedocarcinomas undergo from moderate to extreme squamous metaplasia and then apparently slough. With the sloughing, the lumina become filled with fatty debris, fatty leukocytes and blood pigment. Particularly with this fatty accumulation, calcific deposits result. Vascular changes are acute; the chronic slow sclerosis following roentgen irradiation does not occur, although this is seen in cases in which combined external and interstitial radiation is used. Squamous metaplasia of the surrounding lobules of the normal breast occurs regularly after interstitial radiation.

After surveying sections from amputated breasts, either by the study of several sections from each tumor or by large sections after the method of Cheatele, the following tumor doses administered by interstitial irradiation alone or by combinations with element pack or roentgen rays were regarded as lethal: 900 (two cases), 940, 1,095, 1,150, 1,165, 1,200, 1,265, 1,300, 1,310 (two cases), 1,380 (two cases), 1,625, 1,800, 1,930, 1,950, 2,060 and 2,400 per cent. Results regarded as questionably lethal (cells remaining, but of doubtful viability) were obtained after doses of 1,020, 1,265, 1,350 and 1,500 per cent. What might have happened to the remaining cells had more time elapsed between irradiation and amputation can only be surmised. The breast that showed questionably viable elements after a dose of 1,500 per cent was amputated four weeks after interstitial irradiation. Definitely sublethal results were obtained with doses totaling 635, 650, 760, 950, 1,000, 1,050 and 1,375 per cent. In the case of the failure with 1,000 per cent and 1,050 per cent doses, the tumors were large, measuring 3.5 by 5 by 8 and 5 by 5.5 cm., respectively. There is little doubt that the failure may be properly ascribed to the difficulties in the accurate seeding of such large tumors. The failure of the 1,375 per cent dose must be due to technical errors since the tumor was not large; there is grave reason to doubt that a properly placed dose as high as 900 per cent will not destroy a cancer of the breast.

An attempt to tabulate the histologic changes following external and interstitial irradiation may be summarized as follows. The difficulty is that the dosage obtained by interstitial irradiation cannot be approached by external irradiation alone. The summary therefore is not a comparison between the effects of two types of irradiation but between two types and two widely different degrees of dosage.

External Irradiation

1. Mainly a vascular change
2. Moderate hydropic swelling of tumor cells
3. Moderate atrophic degeneration

4. Marked collagen swelling
5. Productive arteritis with thrombosis
6. Calcific deposits in vessel walls
7. Productive fibrosis

Interstitial Irradiation

1. Mainly a direct effect on the tumor cell
2. Ballooning degeneration
3. Hydropic swelling



Fig. 27.—Whole section of a breast involved by mammary cancer, which had been given preoperative external and interstitial irradiation. The tumor was completely necrotic. The small black areas represent persistent ducts lined by squamous metaplastic cells.

4. Giant nuclei and atypical degenerative mitoses.
5. Tendency toward squamous metaplasia followed by sloughing
6. Hemorrhages, infiltration by fatty macrophages with ensuing extensive calcific deposits
7. Acute capillary necroses with resultant tumor necroses
8. Squamous metaplasia of the normal, adjacent lobules of the breast
9. Collagen swelling, productive fibrosis and late atrophy of the residual tumor

Cancer cells may recover from some nuclear damage, as can be witnessed by the late resumption of growth, but when pyknosis, hydrops and karyorrhexis occur in pronounced form, the immediate or eventual death of the cell is assured.

B. PRIMARY INOPERABLE CARCINOMA OF THE BREAST

All patients with malignant neoplasms of the breast who apply to the Breast Clinic of the Memorial Hospital are classified and assigned to one of several groups, named in the descending order of frequency: recurrent inoperable, primary inoperable, primary operable and recurrent operable carcinomas of the breast. An additional group, termed "prophylactic," is made up of postoperative patients without clinical evidence of cancer, who have been referred for irradiation to the breast wound and drainage areas. The criteria of inoperability are: (1) definite fixation of the tumor to the thoracic wall; (2) marked involvement of the axillary nodes on the same side as the breast lesion, with extension well up beneath the clavicle; (3) definite fixation of the axillary nodes to the thoracic wall; (4) well marked fulness of the supraclavicular region of the involved side; (5) palpable supraclavicular nodes; (6) firm nodes easily palpable in the opposite axilla or the opposite supraclavicular space; (7) evidence of metastasis in the other breast; (8) diffuse extensive invasion of the skin with or without cutaneous nodules; (9) evidence of metastasis to the pleura, lungs or mediastinum; (10) evidence of metastasis to the bones, and (11) metastasis to distant organs, such as the liver, the brain, etc.

The futility of surgical intervention as a curative measure for these advanced carcinomas is manifest. The only possible sphere for operation in the management of these primary inoperable cases lies in the palliative operation (simple mastectomy) after adequate irradiation. Such an operation is indicated when ulceration is present or imminent, or when the bulk of the tumor is distressing to the patient. Following such a removal and the subsequent skin-grafting, roentgen treatments are given when indicated.

Irradiation is now generally regarded by the medical profession as the only worth while method in the treatment for primary and recurrent inoperable carcinomas of the breast. We are justified in believing that when a large portion of the active disease is made stationary or regressive, the patient will be better able to combat the other metastatic lesions. In the event that the cancer is so extensive as to be obviously incurable, irradiation should not be too vigorous, else the bodily resistance to the disease may be greatly lowered. External irradiation has been the procedure of choice in the treatment for these cases during past years; it

is still the only possible means in the treatment for metastases to the bones, lungs, brain and skin. So long as the tumors in these locations continue to regress, further irradiation is withheld. Another series should never be given solely because the skin is in a condition to tolerate it. On the other hand, a second series of treatments (roentgen rays or radium element pack) may be given at the end of six weeks if no definite change has taken place in the tumor or it has ceased to regress, and providing the patient's general condition remains satisfactory.

One important reason for accepting cases of advanced mammary cancer for radiation treatment lies in the fact that occasionally a case of this type may give a far better result following palliative irradiation than one could have hoped for when the patient was first seen. We recently performed a necropsy on a woman who had been kept alive for six and one-half years by the proper palliative irradiation of an inoperable mammary cancer. Another patient, aged 56, had an enormous tumor, 14 by 12 by 10 cm., situated in the axillary tail of the left breast. The microscopic diagnosis was carcinoma. Large, soft, discrete lymph nodes were also palpated in the left supraclavicular space. Six weeks later, following one cycle of treatments by the 4 Gm. radium element pack at 6 cm. distance for 16,000 milligram hours to each area, the supraclavicular nodes had disappeared, and the primary carcinoma had diminished until only a small nodule less than 2 cm. in size remained; interstitial irradiation will be given. Fortunately, the more rapidly growing and early metastasizing carcinomas are usually radiosensitive in similar degree, which accounts for these favorable responses in seemingly hopelessly advanced cases.

Some of the patients with the acute inflammatory type of mammary cancer do very well for a considerable period following appropriate irradiation. The explanation for the failure of surgical intervention lies in the diffuse invasion of the dermal lymphatics. Almost any line of incision passes directly through invaded lymphatic vessels and venules with no barrier to prevent immediate recurrence or wide dissemination.

Whenever inoperability is due to fixation of the primary tumor to the thoracic wall or to the state of the axillary nodes, we employ the same procedure in radiation treatment as obtains for the primary operable mammary cancers, namely, external irradiation followed by interstitial irradiation in properly measured dosage (table 13). The method constitutes the nearest approach to the successful treatment for inoperable mammary cancers, and is handicapped only by the inaccessibility of metastases in the liver, lungs and bones. The delivery of proper tissue doses of irradiation by interstitial means, for the first time affords the hope of curing certain inoperable carcinomas of the breast.

Localized shotty subcutaneous nodules in the thoracic wall are treated first by blanket external irradiation and then by the implantation of gold radon seeds of from 1 to 2 millicuries in strength beneath these nodules. A barrage of these gold seeds is sometimes placed around or in advance of progressive cutaneous metastases or extensions.

Complete dissection of the supraclavicular area to remove metastases in nodes cannot be done without division of the clavicle, which seems a surgical measure not to be recommended because there are probably extensions of the disease beyond the supraclavicular area. Likewise, the presence of axillary nodes with extension well up behind the clavicle is the precursor of supraclavicular involvement. Interstitial irradiation of the supraclavicular nodes even when they are surgically exposed, is sometimes attended by an intractable neuritis, which may persist for many months. The introduction of gold seeds into these nodes must be done cautiously, and the dose must be less per cubic content of tissue than for metastases in the axillary lymph nodes. Repeated external irradiation of the supraclavicular space, even when no palpable disease is present in this location is followed by an immediate puffiness and a later fibrous formation which obliterates the fossa and simulates the presence or persistence of cancer.

Metastasis to the sternum is of frequent occurrence. Our experience indicates that this localization of metastatic mammary cancer is favorable, because of the effectiveness of radiation therapy. One patient has remained well for six years, and another patient presents no evidence of recurrence four years after external irradiation to sternal metastases which appeared subsequent to mastectomy. We can offer no explanation for the relative radiosensitivity of mammary cancer metastatic to the sternum. Radium seems to be more effective than roentgen rays in the treatment for these lesions.

The irradiation of metastases to bone serves three purposes; it may cause an immediate subsidence of pain; it may induce a partial regression of the metastatic carcinoma, and it may stop destruction of bone. When properly administered treatments by radium or roentgen rays are given to these metastases, the reparative osteogenesis often proceeds without delay. In fact, pathologic fractures through metastatic bone lesions from primary mammary cancer can heal with good formation of callus, following these treatments, a phenomenon also observed for the pathologic fractures of certain primary tumors of the bone, such as the endothelial myeloma of Ewing and the benign giant cell tumor. A patient who presents multiple or disseminated metastases to bone obtains a greater regression in these metastatic lesions by irradiation than one who presents a single metastasis to bone. The reason for this difference is that the type of tumor that metastasizes widely to several bones is usually a cellular, anaplastic, small cell. radiosensitive carcinoma.

TABLE 13.—*Measured Tissue Dosage in the Irradiation of Primary Inoperable Carcinoma of the Breast*

Patient and Age	Axillary Ade-nopathy	Size	Cause of Inoper-ability	Operation	Roentgen Treatments	Radium Element Pack Treatments	Inter-stitial Treat-ments	Tissue Dosage in Breast, per Cent, Skin Erythema Doses			Other Irradiation	End-Results	Pathologic Histology
								X- Rays	Radium Element Inter- stitial	Total			
S. G. 46	+	9.5×7.5 cm.	Metastases to skin	1/15/30, local mas- tectomy	12/23/29, 2 high volt- age treat- ments	9/20/29, 16,000 mg. hr. at 6 cm.	65	25	..	Axilla and supraclavicular region by x-rays and radium element pack	10/30/30, died	Infiltrating carcinoma of the sweat gland; productive fibrosis; hydropic degeneration and acidophilic changes in tumor cells; vascular lesions
A. M. 44	+	5.7×3 cm.	Supra-clavicular node	6/15/28, local mas- tectomy	5/4/28, 2 high volt- age treat- ments	140	6/15/28, right axilla 23.4 mc. in gold seeds	4/12/30, metastases to the lung; tumor in breast, 2×2 cm.	Five weeks after irradiation, carcinoma simplex, grade 2 radioresistant; much necrosis and fibrosis
B. C. 53	+	Right, 8×6 cm.	Bilateral tumors in breasts	10/12/28, right local mas- tectomy	2/24/28, 2 high volt- age treat- ments	90	Axilla by high voltage x-rays	5/26/30, died	Right breast, dense fibrosis, sclerosis of vessels, no tumor; left breast, abortive fibrosis, strands of carcinoma in scar tissue
	+	Left, 7×5 cm.		3/29/29, left local mas- tectomy	1/21/29, 2 high volt- age treat- ments	155					
L. H. 52	+	8×5.5 cm.	Supra-clavicular node	8/1/29, 4 high volt- age treat- ments	6/14/29, 16,000 mg. hr. at 6 cm.	150	40	...	Axilla by x-rays; supra-clavicular space by radium element pack	Tumor uncon- trolled; 12/8/29, died	
H. N. 52	+	2.25×1 cm.	Supra-clavicular node	6/1/28, local mas- tectomy	5/2/28, 3 high volt- age treat- ments	225	Left axilla by x-rays and radium element pack; 20 mc. in gold seeds	1930, no evidence except pain in axilla	Three weeks after irradiation; large cells in last stage of regression; infiltrating carcinoma
A. B. (O) 55	+	4.5×4 cm.	Supra-clavicular nodes	4/13/28, local mas- tectomy	11/11/27, 3 high volt- age treat- ments; 1/7/28, 2 high volt- age treat- ments	150 120	Axilla and supraclavicular region by x-rays and 31 mc. in gold seeds	6/24/29, died	Small cell alveolar carcinoma simplex invading lymphatics; wide fibrosis; viable tumor cells

M. S. 49	4×3×2 cm.	+	Metastasis to lung	1/3/30, local excision	6/7/29, 2 high voltage treatments	6/10/29, 16,000 mg. hr. at 6 cm.	6/3/29, 10 mc. in gold seeds	150	90	350	550 in 7 days	Chest and axilla by x-rays	No evidence of tumor in breast; metastases to chest larger	Four months after irradiation; infiltrating duct carcinoma, mostly gelatinous
R. R. 51	9×8 cm.	+	Metastasis to bone and lung	9/6/29, 76.28 mc. in 29 gold seeds	700	700	X-ray pelvic cycle: left axilla by radium element pack plus 40 mc. in gold seeds	Tumor of breast diminished one-half in size by 11/20/29; 9/17/30, died	
E. L. 60	4×3.5 cm.	+	Metastasis to spine and pelvis	7/12/29, 3 high voltage treatments	7/24/29, 25.4 mc. in 11 gold seeds	140	..	560	709	Axilla, spine and pelvis by x-rays	10/13/30, no evidence in breast or axilla; metastases inactive	
E. P. 48	2 masses 4.5×2.5 cm. and 2.5×2.5 cm.	0	Metastasis to lung	Biopsy after irradiation	11/7/29, 42.4 mc. in gold seeds (as 3 spheres)	900	900	11/7/29, 28.4 mc. in gold seeds in right axilla	Tumor almost completely gone; gain in weight	Biopsy after irradiation; few isolated hyperchromatic cells in dense scar tissue
E. H. 64	6×6 cm.	+	Supra-clavicular node	Biopsy before irradiation	7/29/29, 1 high voltage treatment	4/27/29, 16,000 mg. hr. at 6 cm.	10/5/29, 45.6 mc. in 19 gold seeds	75	50	850	Cannot be added	Left axilla by x-rays and radium element pack plus 45.4 mc. in gold seeds	Regression; tumor smaller; disease inactive	Biopsy before irradiation; infiltrating carcinoma, small cells, grade 2 plus radiosensitive
S. M. 45	10×9×5 cm.	0	Metastasis to lung	2/7/30, local mastectomy	1/10/30, 99.5 mc. in 42 gold seeds	1,000	1,000	Left axilla by 20 mc. in 12 gold seeds	Sloughing wound; note short interval between irradiation and operation	Fibrosarcoma
B. K. 67	5.5×4 cm.	+	Diabetes nephritis	Biopsy before irradiation	10/11/29, 47.5 mc. in 23 gold seeds	1,000	1,000	Right axilla by 9.7 mc. in 6 gold seeds	No evidence (5/12/30); scar in breast; recurrence in axilla (7/23/30)	Biopsy before irradiation; small cell infiltration carcinoma, duct type, radiosensitive
C. R. 68	4×2.5 cm.	0	Metastasis to bone and lung	9/24/29, biopsy	6/4/29, 3 high voltage treatments	9/24/29, 27 mc. in 10 gold seeds	140	..	960	1,100 in 1 mo.	Right axilla by x-rays	Epidermoidal dose; no evidence of cancer	Biopsy after external irradiation; fibrocarcinoma
A. S. 58	5.5×4 cm.	+	Intra-clavicular node	3 high voltage treatments	9/21/29, 43.4 mc. in 15 gold seeds	235	..	930	1,165 in 1 mo.	Left axilla by 10.4 mc. in gold seeds; left infraclavicular space by 5.2 mc. in 2 gold seeds	Complete disappearance of all tumors in breast, axilla and infra-clavicular space	

TABLE 13.—*Measured Tissue Dosage in the Irradiation of Primary Inoperable Carcinoma of the Breast—Continued*

Patient and Age	Axillary Ade-nopathy	Cause of Inoper-ability	Operation	Roentgen Treatments	Radium Element Pack Treatments	Inter-stitial Treat-ments	Tissue Dosage in Breast, per Cent, Skin Erythema Doses			Other Irradiation	End-Results	Pathologic Histology
							X- Rays	Radium Element Pack	Inter-stitial			
R. P. 37	+	Metastasis to bone and lungs	1/22/30, biopsy	1/23/30, 3 high volt-age treat-ments	1/22/30, 70 mc. in 25 gold seeds	145	..	1,130	1,275 in 10 days	Radiosensitive; complete disappearance of tumor	Biopsy before irradiation; small cell, highly malignant, infiltrating duct carcinoma
A. B. (2) 73	+	Hilar lymph nodes	10/5/29, biopsy	9/26/29, 33.65 mc. in 11 gold seeds	1,360	1,360 Right axilla by 13.7 mc. in gold seeds	Tumor replaced by scar; disappearance of axillary nodes	Biopsy ten days after irradiation; carcinoma in scar tissue
J. F. 48	0	Metastasis to lungs	9/28/29, biopsy	9/11/29, 16,000 mg. hr. at 6 cm.	9/28/29, 32 mc. in 6 gold seeds	...	60	1,300	1,360 in 19 days	Only thickness of breast remains; local cure	Biopsy seventeen days after external irradiation; adenocarcinoma in walls of dilated ducts
A. F. 37	+	Inflammatory type	11/11/29, 3 high volt-age treat-ments	11/27/29, 87.5 mc. in 47 gold seeds	60	..	1,400	1,460 in 23 days	Regression; tumor quite small	
M. B. 58	+	Metastasis in lungs	11/6/29, local mas-tectomy of right breast	11/6/29, 60 mc. in 36 gold seeds in left breast	1,720	1,750 0	Tumor in left breast almost disappeared	Right breast amputated; bulky adenocarcinoma, grade 3, radio-sensitive
C. K. 73	+	Bilateral axillary nodes	3/20/30, local mas-tectomy for radium ulcer	1/31/30, 3 low volt-age treat-ments	2/4/30, 119 mc. in 71 gold seeds	150	..	2,000	2,150 in 9 days	4/2/30, died; enormous radionecrotic ulcer on chest	Radium ulcer; in base were scattered scar tissue
M. C. 63	0	Cardiac disease	12/21/29, biopsy	12/21/30, 44 mc. in 20 gold seeds; 1/31/30, 32 mc. in 15 gold seeds	2,200	2,200 0	Tumor quite small, hard, fibrous, quiescent	Biopsy before irradiation; small cell duct carcinoma, grade 2; radio-resistant; infiltrates fat and fibrous tissue
E. F. 62	+	Metastasis to lungs, diabetes	6/17/29, 3 high volt-age treat-ments	9/14/29, 16,000 mg. hr. at 6 cm.	11/1/29, 52 mc. in gold seeds	230	50	2,200	Cannot be added	Tumor inactive, hard, fibrous lump, 2 cm.; metastases to lung stationary	

CASE 9.—*To illustrate the use of measured tissue doses of irradiation in the treatment of patients with inoperable mammary cancer.*

A. S., a colored widow, aged 58, applied to the Memorial Hospital on Aug. 28, 1929, complaining of a rapidly growing lump in the left breast. She had one child, now aged 26, whom she had nursed for one year without lactational difficulties. She had had four miscarriages. The menopause had occurred in 1916. In May, 1928, she first felt a lump in her left breast; this lump had increased rapidly in size during the six months prior to admission. On physical examination, the right breast was atrophied. The upper median segment of the left breast contained a hard, delimited tumor measuring 5.5 by 4 by 4 cm. There was definite fixation to the

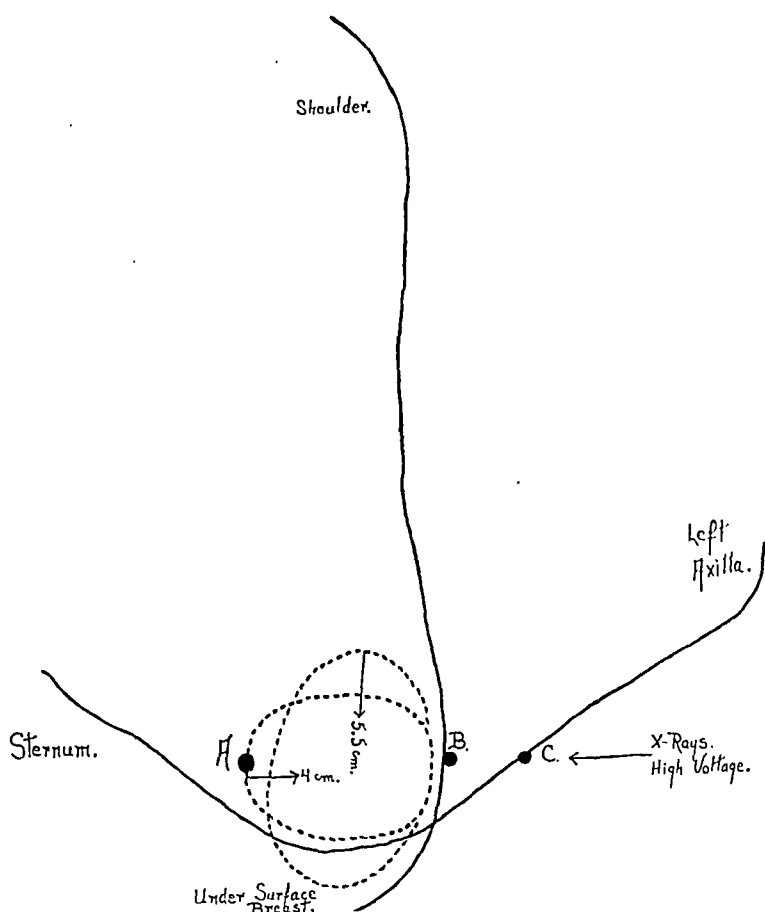


Fig. 28 (case 9).—Graphic representation of superimposed transverse and vertical contours of the left breast, illustrating the estimation of the depth of dosage by external irradiation.

superjacent skin, and the left nipple was contracted. The left axillae contained discrete large lymph nodes; there was one fixed hard nodule in the left infraclavicular space. A roentgenogram of the chest showed a very small nodular mass in the right hilus, which was interpreted as an early metastasis. The clinical diagnosis was primary inoperable carcinoma of the breast with metastases to the left axillary and infraclavicular nodes.

Immediate treatment was instituted, a high voltage roentgen cycle being applied to the left breast with drainage areas (from August 29 to September 17). This was followed on September 21 by the implantation of 15 gold radon seeds contain-

ing 43.43 millicuries in the mammary tumor, 4 gold seeds containing 10.4 millicuries in the left axilla and 2 gold seeds containing 5.2 millicuries in the infraclavicular node. The mammary tumor received a total of seven skin erythema doses in its depth. All palpable evidence of this mammary cancer had disappeared by October 21; the patient remained free from local recurrence in the irradiated area, but there has been some increase in the number and density of the peribronchial shadows.

Comment.—Primary inoperable mammary cancers may be treated by properly measured doses of irradiation in sufficient quantity to insure the disappearance of cancer in the breast and adjacent lymph nodes. This method constitutes the procedure of choice and is the only available measure for palliation and possible cure for inoperable carcinomas of the breast (fig. 28).

C. RECURRENT CARCINOMA OF THE BREAST

Few recurrent carcinomas of the breast are operable. During the last twelve years, 2,234 patients with carcinoma of the breast were treated at the Memorial Hospital; less than 50 of these patients had recurrent operable cancers. We define a recurrent operable mammary cancer as a single, freely movable tumor recurring in the operative field.

On the other hand, patients with recurrent inoperable carcinomas of the breast constitute the largest division or group admitted to the hospital, according to our plan of classification. The cases of recurrent inoperable carcinoma, of necessity belong entirely to the field of radiology, for radiation therapy offers the only hope of arresting or eliminating the disease or relieving many of its distressing symptoms. Frequently the recurrences together with possible distant metastases are too widespread for effective radium therapy. The presence of the operative scar and the multiplicity of the lesions militate against successful irradiation. When the breast has been amputated, a most valuable holder for interstitial irradiation is thereby lost. Recurrences in the wound or scar are in such close approximation to the thoracic wall that great caution must be exercised in the implantation of gold radon seeds, else the ribs will be injured by the radiations. The disappearance of the diffuse cutaneous recurrences of inflammatory carcinoma of the breast after roentgen treatment is striking. Diffuse recurrences are treated by roentgen rays rather than by the radium element pack for two reasons: the area of skin exposed can be larger, and the depth of the dose in the skin and subcutaneous tissues can be appreciably greater (table 3). In instances in which the recurrence is well localized, the radium tray, at 3 cm. focal distance, is applied for a dosage of from 3,000 to 3,500 millicurie hours. We have treated many patients with localized recurrent carcinomas by measured tissue doses of irradiation, using external irradiation followed by the implantation of gold radon seeds.

Recurrent carcinomas ulcerate quickly. The ulcer may spread widely, remaining superficial. We have had considerable success in treating these large superficial ulcers by unfiltered or very lightly filtered (from 1 to 2 mm. aluminum) roentgen rays, which stimulate rapid healing.

Late Changes in the Skin Following Irradiation.—When the low voltage type of roentgen treatment was given over a long time, especially in the primary inoperable cases, considerable atrophy of the skin and small telangiectases would sometimes appear two or three years later. In many cases these have increased in size and number, often covering the entire irradiated area; the extreme complication is ulceration and the supervention of squamous cell epithelioma. This necessitates wide excision of the leathery skin and subsequent skin-grafting. Our experience has led us to believe that small doses of irradiation repeated at intervals over a long time are far more likely to cause these changes than a single massive dose from which the skin recovers quickly with little resultant damage and no late complications. Our present method of administering all the radiation therapy in less than three weeks is not attended by significant late changes in the skin.



Fig. 29.—(A) Flat, superficial, ulcerated recurrent carcinoma of the left breast. (B) Clinical disappearance of recurrent tumor with epithelialization following two treatments by unfiltered roentgen rays.

Local Excision and Irradiation in Selected Cases of Mammary Carcinoma.—In general, we do not approve of the principle of local excision and irradiation of mammary cancer. In certain cases, however, this procedure has been carried out with success, notably whenever the original clinical diagnosis was mastitis or fibro-adenoma, and a frozen histologic section and microscopic diagnosis revealed carcinoma but the patient refused the complete operation; and whenever local wide excision of a suspicious lump in the breast was followed by the diagnosis of encapsulated papillary intraductular or papillary intracystic carcinoma, with no evidence of infiltration. Radical mastectomy is the procedure of choice, for though the carcinoma is of low grade malignancy and appears to have been excised completely, the possibility always remains that new carcinomas of similar structure may originate in other ducts or cysts within the same breast. In the event that the complete operation is not done and no regional metastases are known to exist, we have inserted

gold seeds widely through and in the fresh wound before suturing, thereby insuring accuracy of placement for the interstitial irradiation; sometimes, however, the healing of the wound is delayed. This is followed by heavy external irradiation (radium element pack or roentgen rays) over the breast and drainage areas.

SUMMARY

1. Preoperative external irradiation for mammary carcinoma is of value, as is proved by: (1) the occasional regression of tumors so treated; (2) the histologic changes produced, and (3) the better clinical end-results.

2. An efficient devitalizing dose cannot be delivered by external irradiation alone.

3. To deliver an efficient dose one must use interstitial irradiation.

4. The tissue dose delivered to the tumor should be measured and expressed in skin erythema units. This dose should be prescribed.

5. Tables prepared in the physical department enable the clinician to translate into terms of skin erythema units the tissue dose delivered, whether by external or interstitial irradiation.

6. The universal tissue dosage necessary to effect destruction of a radioresistant mammary cancer approximates twelve skin erythema doses.

7. The safest procedure is to treat all patients with mammary cancers with the same sufficient dose, because (1) radiosensitivity cannot always be determined before operation, and (2) the same tumor may contain radioresistant and radiosensitive areas.

8. Mammary cancers vary markedly with respect to radiosensitivity.

9. The mammary gland will tolerate safely an enormous dose of interstitial irradiation.

10. The possible menace of dissemination of the disease by the method of interstitial irradiation has been considered. We have not seen evidence of such a dissemination in this series. Preliminary external irradiation lessens this possibility.

11. All preoperative irradiation should be given within three weeks or less time.

12. Six weeks should elapse following interstitial irradiation before radical amputation is performed.

13. An interval of six weeks is necessary, because after this interval (1) the effects of irradiation are complete, (2) complete destruction of the tumor is accomplished and (3) wound healing is unimpaired.

14. Our present treatment for primary operable mammary cancer is external irradiation, then interstitial irradiation and finally radical amputation six weeks later.

15. The axilla is irradiated by (1) preoperative roentgen rays or radium element pack, followed by (2) interstitial gold-filtered radon distributed along the gland-bearing areas.

16. The pathologic changes produced in mammary cancer by external irradiation are mainly due to vascular effects. There are moderate hydropic swelling of the tumor cells, moderate atrophic degeneration, marked collagen swelling, productive arteritis with thrombosis and calcific deposits in the vessel walls and productive fibrosis.

17. The changes produced by interstitial irradiation are mainly direct effects on the tumor tissue, namely, ballooning degeneration, hydropic swelling, giant nuclei and atypical degenerative mitoses, a tendency toward squamous metaplasia followed by sloughing, hemorrhage, infiltration by fatty macrophages with ensuing extensive calcific deposits, often acute capillary necrosis with resultant tumor necrosis, squamous metaplasia of normal adjacent lobules in the breast, collagen swelling, productive fibrosis and late atrophy of the residual tumor.

NOTE.—In the continuation of this study, all new cases of primary operable carcinoma of the breast are divided into three categories for the purpose of evaluating the different methods of treatment, namely: (1) surgical intervention alone, (2) external and interstitial irradiation followed by surgical intervention and (3) irradiation alone. The patients for these groups are not selected, but are assigned in the order of their application to the clinic. Time will reveal the relative effectiveness of these procedures.

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DISEASES OF THE LARGE INTESTINE*

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Diseases and abnormalities of the large intestine are far too numerous to be described in one paper; I shall discuss, therefore, only the more common conditions that may be encountered in the routine examination of the gastro-intestinal tract.

The normal contour and position of the colon, as well as many of the abnormal positions that it may assume, are familiar to all physicians. It may not be so well known, however, that a transverse colon that crosses the upper part of the abdomen is more or less rare. In the majority of cases, one finds that the colon falls well below the umbilicus, and it is not unusual to find a transverse colon with its midpoint below the urinary bladder. In many cases the rotation of the colon is incomplete; frequently the embryonic stage is not fully resolved. The normal sigmoid flexure is generally from 16 to 17 inches long (40.6 to 43.1 cm.), but this length may vary, a redundant sigmoid sometimes being several feet in length. Doubtless some cases of obstipation are due entirely to this redundancy. The dilated colon, also, is often a source of difficulty. At the present time, extensive work is being done in an effort to prove that, in some cases at least, colonic stasis is directly responsible for arthritis, stasis being apt to occur, of course, when the colon is dilated, spastic or redundant. The intestinal activity is accelerated in the presence of hyperthyroidism, and diarrhea may be expected to occur; conversely, hypothyroidism is held responsible for hypomotility of the intestines, with its accompanying symptoms of constipation and toxemia.

SPASTIC COLITIS

The etiology of spastic colitis has not been ascertained, although many theories have been advanced to account for the syndrome designated by this name; some writers even argue that it is not a definite condition, and many competent clinicians ignore its existence completely. It is my belief that spasticity of the colon is a real entity and one that can be definitely demonstrated. In the majority of cases, the condition does not become serious, although at times it causes alarming symptoms which may be readily misinterpreted. This misinterpretation occurred, in fact, in two cases that recently came under my observation.

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* From the Cleveland Clinic.

In one of these cases the roentgenogram showed a constant filling defect in the sigmoid flexure. At operation, the only finding was spasticity in the area of the roentgenographic deformity. In the other



Fig. 1.—Roentgenogram illustrating a case of stone in the appendix of a child. This was a retrocecal appendix that had ruptured. The arrow points to the stone.

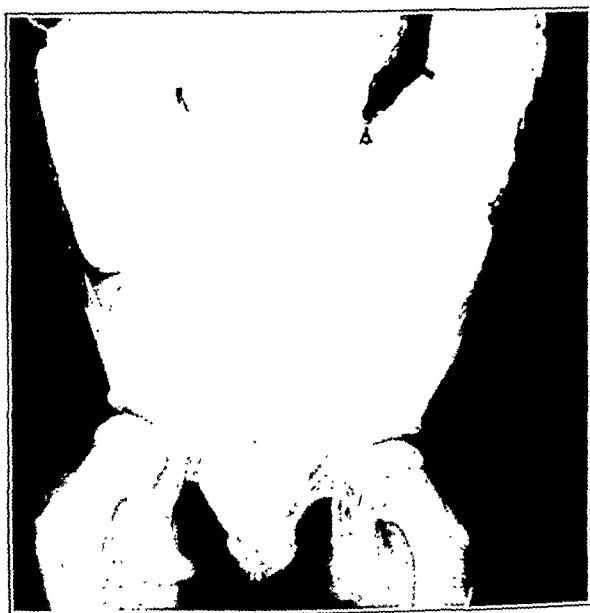


Fig. 2.—Megacolon in a child. Note that the colon almost entirely fills the abdomen.

case the same principle was illustrated, although the spastic area was not in the colon. All the cardinal symptoms of complete intestinal obstruction were present in the latter case, and consequently an opera-

tion was performed. The patient died on the operating table, and at autopsy a spastic area in the jejunum was disclosed. Had a test been made with atropine or some other antispasmodic, doubtless an operation would not have been performed and the patient would still be alive.

Spastic colitis is a functional condition that may give rise to numerous symptoms, the most common of which are constipation, flatulence, abdominal malaise and pain (either localized or general). If the spasticity persists, it may lead to an inflammatory change with

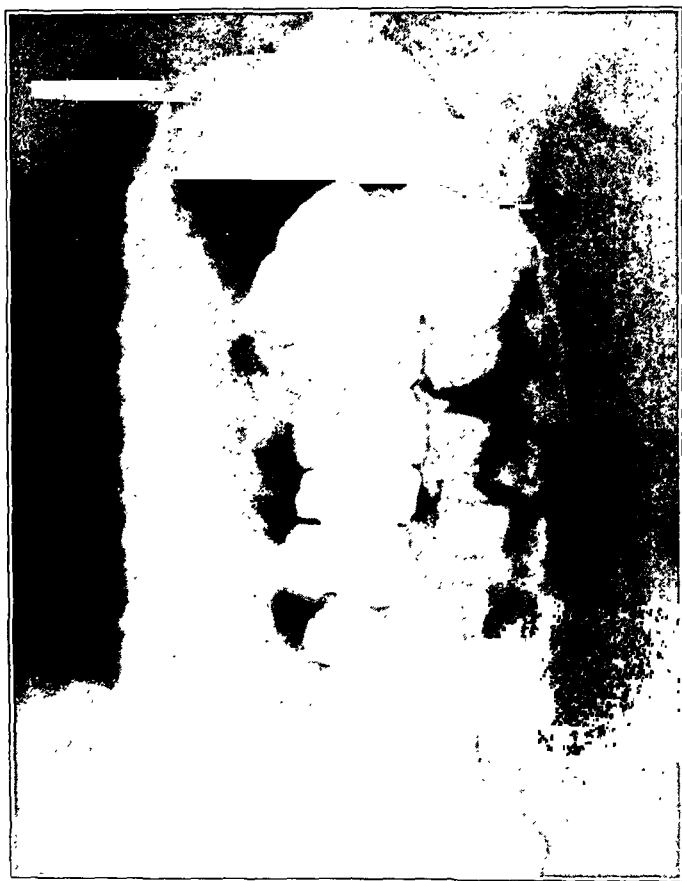


Fig. 3.—Roentgenogram showing a portion of the colon herniated high into the left pulmonic field.

its accompanying symptoms. Since constipation is the most constant symptom, it is surprising to learn that often there is marked colonic hypermotility, the head of the barium meal reaching the rectum in a few hours. This is not difficult to understand, however, in view of the mechanism that causes spastic colitis. According to Gauss,¹ several theories have been advanced to explain hypertonicity. Among these theories are those of an unstable nervous system, a submerged

1. Gauss, H.: The Spastic Colon, *Ann. Int. Med.* 3:1128, 1930.

fear complex acquired in early life and an inherited spasmophilic tendency. "The direct etiologic factor is an open problem today. Nevertheless, it has been observed that usually the patient with a spastic colon is a neurotic individual given to introspection, and that the hypertonicity of the colon is a local manifestation of a general spasmophilic tendency." Spasticity, no doubt, is the underlying cause, this being due to a variable degree of reflex contraction of the smooth muscle fibers.

ULCERATIVE COLITIS

It is probable that ulcerative colitis is caused by an infection that has been superimposed on tissues the resistance of which has been



Fig. 4.—Roentgenogram showing an abnormal position of the proximal colon. Scarcely any of the colon is seen to the right of the midline. The cecum and appendix are low in the pelvis.

lowered as the result of a predisposing condition, such as long-standing catarrhal inflammation of the bowel or severe spasticity of the colon. The ulcerations vary greatly in size, some being only as large as a pin-head while others completely surround the lumen of the colon. Some ulcerations may be very superficial, becoming completely healed in a few days, while others may extend to the muscular coat or may even penetrate the wall of the colon and involve the peritoneum.

The disease is apt to be sudden in its onset, with lancinating pains over the course of the colon, accompanied by griping and frequent bowel movements. There are severe constitutional disturbances, and

in those cases in which the disease is progressive, despite treatment, the resulting mental condition parallels the effect of the toxemia on the nervous system. These attacks occur in cycles, and between them the patient has complete comfort. After a few attacks, mucus, pus and blood are passed, and in severe cases the condition of the patient is distressing.

Ulcerative colitis may be confused with dysentery, typhoid fever or a malignant condition. It presents many of the characteristics of the later stages of bacillary dysentery, but is not so fulminating in its onset and does not produce profound toxemia, and the fever seldom is as high as in the former condition. The final differentiation, however, depends on the results of stool cultures and agglutination tests. Amebic dysentery is more gradual in its onset; it presents stools con-

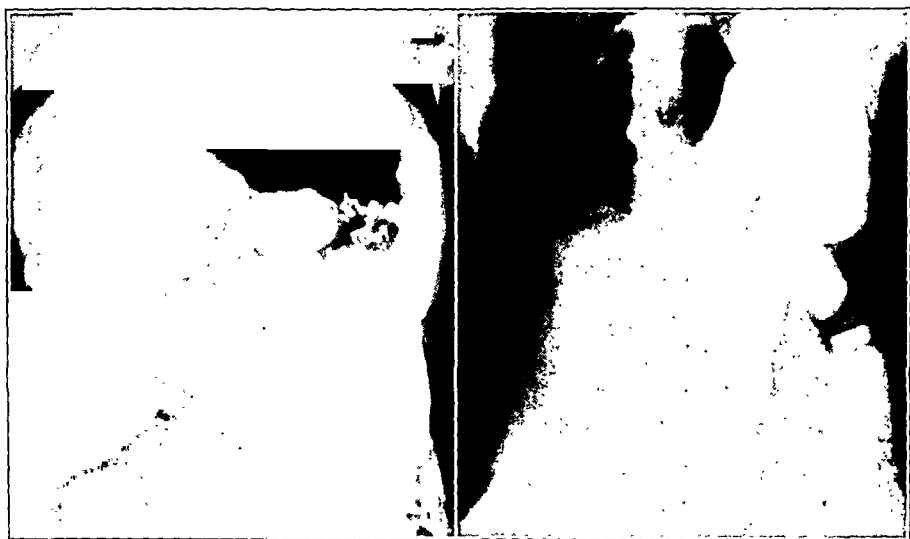


Fig. 5.—Roentgenograms showing hernia of the diaphragm on the left.

taining amebae and gray, blood-stained or yellow mucus, and the condition of the patient is improved after three or four days of treatment with emetine hydrochloride. In this country, chronic bacillary dysentery is less common than is chronic ulcerative colitis, and its diagnosis is made by agglutination tests. Examination with the sigmoidoscope may reveal tumors or ulcers in the rectum and permit the obtaining from them of mucus, a slough or a scraping for examination or culture. A roentgenogram may be helpful in the recognition of colitis by revealing the presence of spasm or areas of ulceration.

Typhoid fever may be differentiated from ulcerative colitis by a history of exposure to a source of infection, followed in two or three weeks by an insidious onset, and at the end of another week by the development of rose spots and enlargement of the spleen. The temperature curve in typhoid fever usually is characteristic, and there are

progressive leukopenia and lymphocytosis. Blood cultures may give positive results as early as the second day, and the Widal reaction is positive after the tenth day.

Cancer develops much more slowly than ulcerative colitis, and pain and griping are rarely seen early in malignant disease. Constipation is one of the earliest symptoms of carcinoma, as is the case in colitis, but



Fig. 6.—Roentgenograms showing varying degrees of redundant sigmoid.

in a case of carcinoma the patient is comfortable after the bowels have moved, except in the late stages of the disease, while in colitis a bowel movement fails to give relief.

PERICOLITIS

The manifestations of pericolicitis vary with the duration of the condition, the type and virulence of the infecting organism and the length of intestine involved. The chief symptoms are constipation, alternating

with occasional diarrhea, constitutional disorders resulting from absorption, localized abdominal soreness or pain on pressure, a palpable abdominal mass, which may readily be mistaken for a tumor, and mucus or blood in the stools. Mild and sometimes alarming symptoms of intestinal obstruction may be present, depending on the degree of nar-

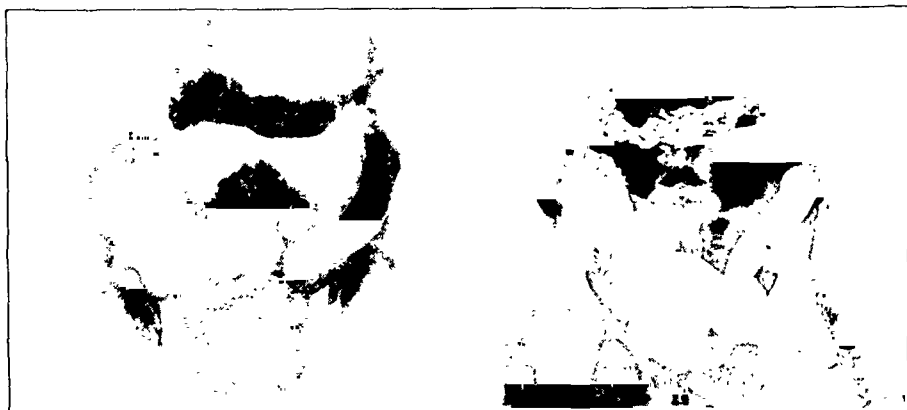


Fig. 7.—Two cases of chronic ulcerative colitis. Note the loss of tone in the colon.



Fig. 8.—*A*, a case of diverticulosis. Note the diverticula along the entire course of the colon. *B*, roentgenogram of a typical colon twenty-four hours after the administration of barium, showing many diverticula.

rowing of the lumen of that portion of the colon involved. In cases in which the temperature is high, an abscess may be suspected.

In obscure cases it is necessary to differentiate between this condition and appendicitis, diverticulitis and cholecystitis. Fluoroscopic examination and roentgenograms following a barium sulphate enema will often aid in making the differential diagnosis, although in diver-

ticulitis the enema is not so important as the twenty-four hour barium examination, since barium sulphate when given by mouth is so much more certain to fill a diverticulum than when given by enema.

APPENDICITIS

I do not mean to imply that all cases of appendicitis can be diagnosed by roentgenograms, but many cases cannot be diagnosed pre-



Fig. 9.—*A*, roentgenogram of sigmoid extending to right lower quadrant. Note several small diverticula in the sigmoid. *B*, diverticulosis of the sigmoid. Note the long loop of sigmoid with evidence of pressure from an extrinsic mass. *C*, roentgenogram showing almost complete obstruction in the sigmoid due to a large inflammatory mass in the area designated by the arrow. The presence of several small diverticula proximal to the lesion is evidence in favor of a non-malignant tumor.

operatively by any other method. Acute appendicitis is not a problem for the roentgenologist, but one that should be handled promptly by

the surgeon. The cases in which roentgenographic study is of value are those in which there is a history of vague abdominal uneasiness or distress, with a digestion that is not up to par. In many instances suspected cholecystitis can be ruled out by the roentgenographic demonstration of incomplete rotation of the colon which leaves the cecum and

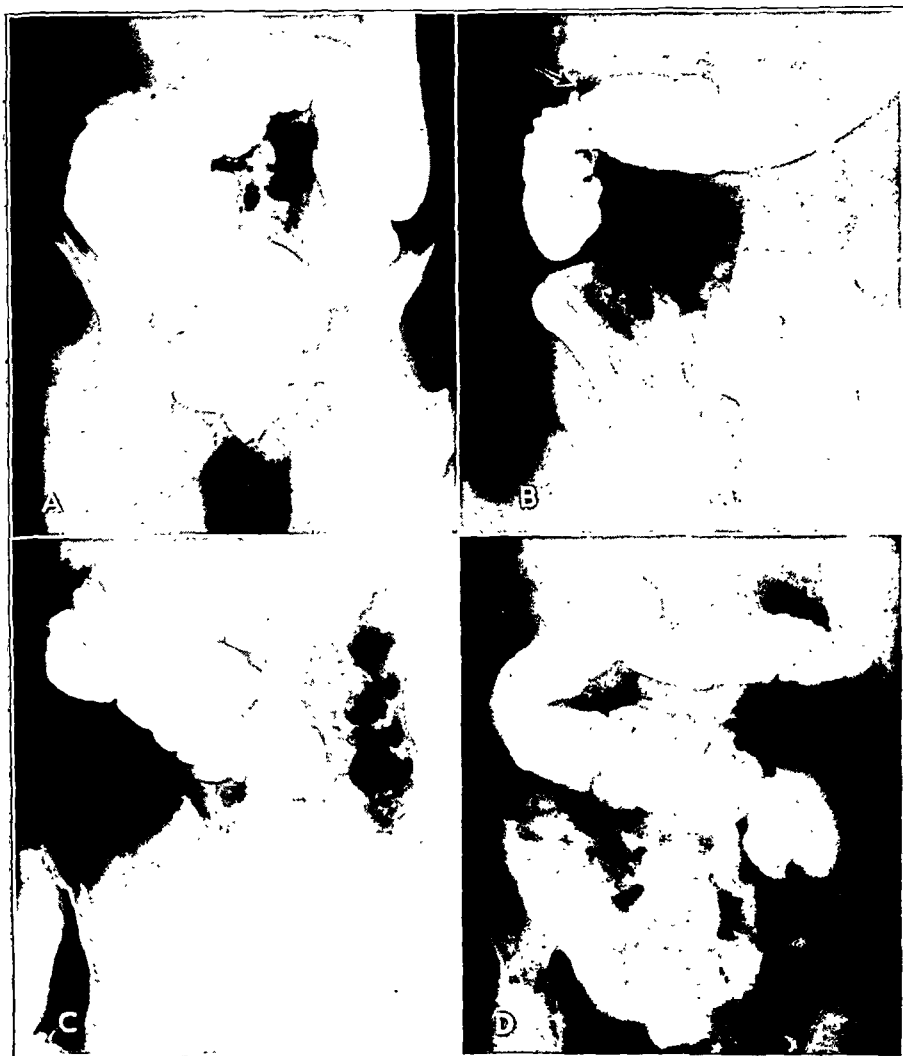


Fig. 10.—*A*, roentgenogram showing the cecum lying high in the right upper quadrant. It is in such cases as this that a diagnosis of appendicitis is difficult. *B*, a similar case. The arrow points to the tip of the appendix lying high under the liver. *C*, roentgenogram showing the cecum lying in the midline. *D*, roentgenogram showing the cecum lying far to the left. Should appendicitis develop in this case, it would be difficult to diagnose. Symptoms would be referred to the lower left quadrant.

appendix in the region of the gallbladder. Often also it is possible to demonstrate the presence of an elongated retrocecal appendix with the

tip high up under the hepatic flexure, a finding that is of value in the differential diagnosis and of assistance to the surgeon in planning his incision. The presence of stones in the appendix also can be demonstrated roentgenographically, as well as adhesions that prevent the free movement characteristic of the normal appendix. In other types of appendiceal disease an irregular filling can be demonstrated that corresponds to definite localized tenderness. It is not often that the appendix is found in the classic McBurney position, but it can be localized accu-



Fig. 11.—Roentgenogram showing a large filling defect in the first portion of the ascending colon due to carcinoma.

rately with x-rays, while pressure will determine the presence or absence of tenderness. Delayed emptying of the appendix (from twenty-four to seventy-two hours after the head of the colon has emptied) is thought by some authorities to be evidence of chronic appendicitis.

FOREIGN BODIES

The presence of foreign bodies can be demonstrated roentgenographically only when they are of opaque material. Serial roentgenograms and fluoroscopic examinations are essential in order to follow

the progress of the foreign body through the intestinal tract and to make sure that it has not lodged at some vulnerable point.

TUBERCULOSIS

Tuberculosis of the colon and rectum may be either primary or secondary. In a review of 100 cases, Gant² found that the infection was secondary in 75 per cent, and that in the majority of these the foci were located in the lungs, larynx or pharynx. Primary tuberculosis of the colon usually develops in the cecum or at the anus, while secondary lesions may be found anywhere in the intestinal tract, although they, too, are found most frequently in the cecum and rectum. Many factors contribute to produce this result, such as the greater speed of the intes-

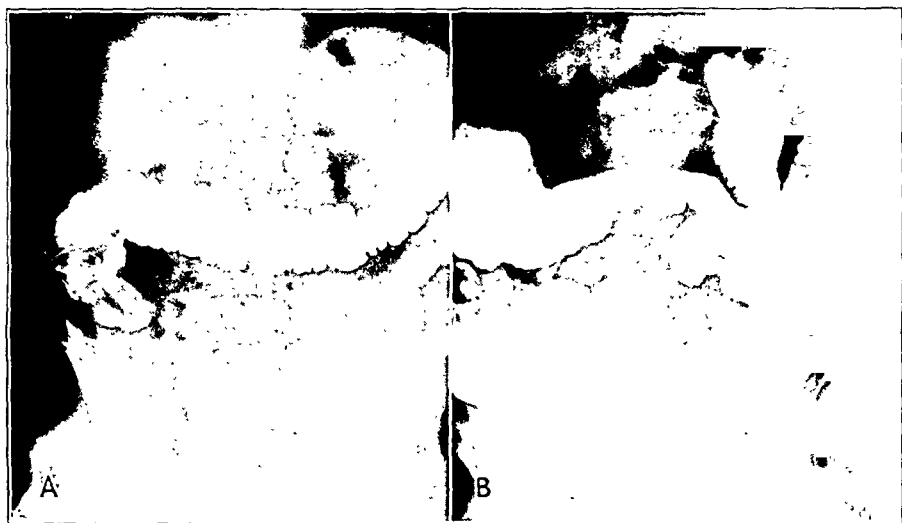


Fig. 12.—*A*, roentgenogram showing a filling defect in the cecum due to carcinoma. *B*, roentgenogram showing a filling defect in the ascending colon due to a large carcinoma.

tinal content through the small bowel, which does not permit the bacilli to find lodgment there; attenuation of the bacilli by the gastric juices, their virulence not being recovered until the cecum or colon is reached; the alkaline reaction of the feces after the ileocecal region is attained, which provides a more propitious environment for the bacilli; the formation of hardened masses of feces in the cecum, which traumatize the mucosa and produce conditions favorable to infection, and the abundant lymphatic distribution in the ileocecal region, which favors the development of tuberculosis.

Several types of tuberculosis are found in the colon, the most common of which are the hyperplastic, ulcerative and miliary.

2. Gant, S. G.: Diseases of the Rectum, Anus and Colon, Philadelphia, W. B. Saunders Company, 1923, vol. 3, p. 43.

Hyperplastic tuberculosis occurs in both children and adults, most frequently in the third decade. It may be primary or it may be secondary to a focus higher up in the intestines or in some other organ. It produces a slow-growing tumor which at times is quiescent for two or three years before it attains sufficient size to occlude the lumen of the intestine and produce symptoms of obstruction. These tumors usually feel smooth when palpated, but examination of a gross section reveals a very irregular, hard and brittle type of tissue. Usually they are fixed, but they may be slightly movable. The rigidity of the terminal ileal segment is a characteristic roentgenographic observation.

In the ulcerative type of tuberculosis, the ulcers may be superficial or deep. Superficial ulceration may heal promptly, but deep ulceration progresses rapidly and is almost impossible to control. The mixed

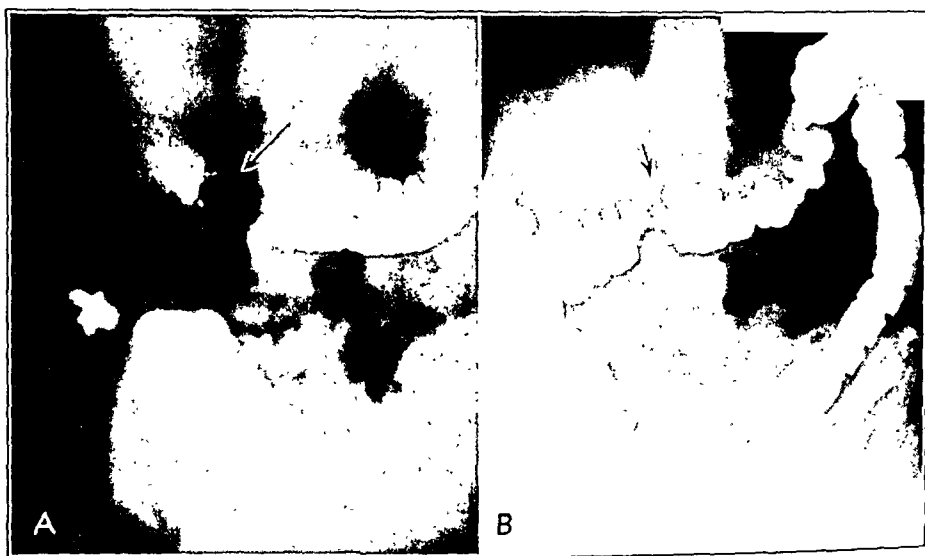


Fig. 13.—*A*, the arrow points to a deformity in the transverse colon due to carcinoma. *B*, a similar case, but less obstruction is present. However, note the beginning dilatation of the colon proximal to the obstructing area.

infection that must follow soon causes toxemia, imperfect digestion, constitutional manifestations, persistent diarrhea and extensive destruction of the mucosa and deeper bowel coverings. Hemorrhage, peritonitis, abscess, adhesions and other serious complications may be encountered, and if surgical intervention were instituted, a generalized miliary tuberculosis of all the abdominal viscera might be found.

The prognosis of intestinal miliary tuberculosis is unfavorable because it is secondary to a well established process elsewhere, and the patient is debilitated and unable to withstand the ravages of the fast-spreading tuberculous process.

DIVERTICULA

A diverticulum is a non-neoplastic outpouching of intestine, having a lumen that connects with the bowel or that formerly connected with it.

Diverticula may be congenital (true) or acquired (false), the latter form appearing more often between the ages of 40 and 60 years, and about twice as frequently in men as in women. Diverticula may develop at any point along the course of the colon, but are found most commonly in the sigmoid flexure, the descending colon, the cecum and the transverse colon. The hepatic flexure also is frequently involved, and diverticulitis at this point is at times most difficult to differentiate.

Diverticula may be single or multiple, large or small, smooth or irregular. The sacs may be quiescent for many years and then suddenly become obstructed, resulting in acute inflammation. Symptoms may then become severe and lead to the belief that appendicitis, peritonitis, intestinal obstruction, a new growth, or an abscess is present. Definite



Fig. 14.—*A*, a filling defect as seen fluoroscopically in the lower descending colon. The loop of the sigmoid obscures the deformed area. *B*, the same case after air has been injected into the colon. The arrow points to a filling defect due to carcinoma.

proof that many diverticula never produce symptoms is presented by the frequent finding of such pouches during the course of routine gastro-intestinal examinations and at autopsy.

Diverticulitis may be acute or chronic, more often the latter. Because of the size, form, consistency and macroscopic appearance of the tumor, a diverticulum often is mistaken for carcinoma. Doubtless many of the supposed carcinomas that have been reported cured by operation have in reality been merely inflammatory masses caused by diverticulitis. It may be that these diverticula are a predisposing cause of carcinoma, but to determine this definitely would require extensive research.

After the onset of inflammation in a severe case of diverticulitis, there will be localized tenderness, intense cramps and constipation with a sensation of blocking. When the lumen is almost occluded there are a marked formation of gas, severe pain, muscular rigidity, nausea and vomiting, an increased temperature and pulse rate and mucus, pus and blood in the stools. If the process progresses to the point of rupture, the usual symptoms of spreading peritonitis are present. If an abscess forms, there is continued localized pain and swelling until it has ruptured into the intestine or peritoneal cavity or has been drained.

Given a history of chronic left-sided inflammation, with periodic exacerbations and an absence of cachexia and loss of weight, a diag-



Fig. 15.—Roentgenogram showing carcinoma of the sigmoid. This could not be seen with the patient lying flat. The film was exposed with the right side of the patient uppermost. The sigmoid is a frequent location for carcinoma. The coils of the lower sigmoid and rectum overshadow these growths.

nosis of diverticulitis usually is justified. Proctoscopic examination may reveal a small opening from which pus is draining, and pus in the bowel is suggestive of diverticulitis.

If the patient's condition is extremely grave, it is not advisable to subject him to a roentgenographic examination. Cases have been diagnosed, however, in which the obstruction was almost complete, a barium sulphate enema showing the filling defect. It is often impossible to make the differentiation on the basis of the roentgen examination alone, but the small cavitation that is present in carcinoma is rarely seen in

diverticulitis. The deformity, of course, is due to narrowing of the lumen of the colon, but in diverticulitis there is, as a rule, no break in the mucosa and the rugae can be seen in the deformity.

CARCINOMA

Unfortunately, early carcinoma of the colon is difficult to diagnose roentgenographically, as a filling defect does not develop until the late stages of the disease. It is impossible to see the early ulcerations, and a mass must be present that will displace a portion of the column of barium sulphate in the colon before a diagnosis can be made. After the growth has become large enough to produce partial obstruction, dilatation of the colon proximal to the lesion will be noticed. In many instances carcinoma of any portion of the colon may be overlooked if redundancies cover up the lesion. A fluoroscopic examination should be made from all angles, therefore, in an effort to throw these redundant loops out of the field of vision and pick up some small filling defect on either the anterior or the posterior wall of the intestine. Patients suffering from early carcinoma of the colon, however, seldom present themselves for roentgenographic examination.

Fully developed cancer of the colon usually produces fairly typical symptoms: alternating constipation and diarrhea, distention of the colon, tenderness, localized abdominal pain, attacks of offensive discharge containing mucus, blood, pus and possibly tissue fragments, loss of weight, cachexia, visible peristalsis and a filling defect, with evidence of dilatation of the colon proximal to this defect. It is often difficult to pass any of the opaque medium through the area of partial obstruction when the barium meal is given by enema, though a small amount may pass the obstruction when the barium meal is given by mouth. Atropine and other antispasmodics offer little assistance in the passage of the enema through the deformed area. When cecal carcinoma is suspected, a delay in ileal emptying is a significant sign. A proctoscopic examination should always be made before a barium sulphate enema is administered, in order to detect any evidence of the disease that may be visible in the rectum or lower bowel. Barium sulphate should not be given before this examination is complete, as it coats the bowel and obscures any evidence of disease that may be present.

OPERATIONS ON THE SUPERIOR POLE OF THE THYROID *

C. A. ROEDER, M.D.

OMAHA

The most successful operations on the goitrous or toxic thyroid comprise the preservation of parathyroid, laryngeal and tracheal function and the removal of enough glandular tissue to allow thyroid function to be controlled by the patient's physiologic reactions or by the administration of desiccated thyroid extract. The accidental injuries to the recurrent laryngeal nerves and parathyroid have encouraged most of the attention of surgeons to the middle and lower portions of the gland.

From observations of my own series of over 1,800 resections of all types of goiters and of many more operated on by other surgeons, I have witnessed an undesirably high percentage of changes in the tone of the voice, i. e., a lower pitch with a decreased range and huskiness, with or without a partial loss and lasting for a varying length of time. Changes in the voice and moderate obstructions to inspiration are generally of short duration and due, in nearly all instances, to a congestion of the mucous membranes of the larynx and trachea, postoperative immobility of the larynx, loss of vocal cord tension and temporary injuries to the superior and inferior laryngeal nerves producing incomplete abductor and adductor vocal cord immobility. During all voice changes, and when particularly prolonged, a hysteroid background must be kept under consideration.

Surgical trauma during resections of goitrous thyroids is often not followed by a corresponding degree of aphonia or laryngeal dyspnea. Surgeons frequently see examples of adductor or abductor vocal cord paralysis in which they feel positive that the inferior laryngeal nerve had not been traumatized in any manner. They have also expected a loss of voice following the removal of deeply lying and adherent adenomas, operations which could hardly have failed to injure the inferior laryngeal nerves, and they have been greatly surprised to hear the patient talk almost as well as ever. These two differing experiences suggest that the innervation of the larynx is at times irregular and not as well understood as one desires. Adductor paralysis results in a loss

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* From the Department of Surgery, University of Nebraska.

* Read in part before a meeting of the state societies of Wyoming, Montana and Idaho, Yellowstone Park, Aug. 12, 1928.

of voice, while abductor paralysis results in laryngeal dyspnea. Both conditions are generally assumed to be due to injury to the inferior laryngeal nerves. Loss of vocal cord tension results in a husky and lower tone of voice, which is often due to paralysis of the cricothyroid muscles innervated by the superior laryngeal nerve. Postoperative changes in the voice, obstructive dyspnea and tetany have turned almost the entire technical attention of surgeons to the middle and lower portions of goitrous thyroids. The object of this paper is to demonstrate that the removal of the superior pole of the thyroid, although easier, may be followed by at least as many complications as resections of any other portion of the gland. The parathyroids are often found lower than the superior pole and are here of less surgical importance. The only parathyroids present, however, may be attached to the superior pole.

THE PRETRACHEAL FASCIA

The thyroid gland is covered anteriorly and laterally by the so-called capsule which is derived from the middle or pretracheal layer of cervical fascia, and has been described by the majority of all authors as enclosing the entire gland. Only by embryologic studies, however, can this be definitely determined. Whether the gland reaches its usual position before the development of the pretracheal fascia or whether the fascia develops before the gland has fully descended are two questions of importance. Both, however, preclude the thought that this fascia surrounds the posterior surface of the thyroid. The dissections of Fowler and Hanson,¹ comprising 200 glands, did not in one instance show this layer of fascia enclosing the posterior and inner surfaces of each lobe. Their findings correspond with those in many of my own surgical dissections, which showed a reflection of this fascia away from the posterolateral border of the gland to encircle the esophagus. Testut² described and illustrated this fascia as just stated. In other words, it is more reasonable to state that the thyroid does not possess a capsule but lies behind the pretracheal fascia, which continues its course the same as if the gland were not present. There is a thin closely adherent capsule developed from interparenchymatous tissue which is of non-surgical use or importance.

The pretracheal fascia apparently folds over the anterior, external and internal surfaces of the superior pole, surrounding it more than any other portion of the thyroid, and binds this portion of the gland to the external lateral surfaces of the laryngeal cartilages and muscles. At the superior pole, therefore, it acts as a three-quarter sheath, and as it continues upward to be attached to the hyoid bone, it more or less

1. Fowler and Hanson: Surg., Gynec. & Obst. **49:59** (Oct.) 1929.

2. Testut: *Traité d'anatomie humaine*, ed. 7, Paris, Gaston Doin, vol. 1, p. 776.

encapsulates the superior thyroid vessels and contains, within a separate compartment on its internal surface, the external branch of the superior laryngeal nerve. As the fascia lies opposite the thyrohyoid membrane, it is attached for several centimeters to the internal branch of the superior laryngeal nerve just before it passes beneath the medial upper border of the inferior constrictor muscle of the pharynx, which border often lies lower than the upper extremity of even the normal superior thyroid pole. Forcibly pulling this fascia downward by traction on the superior pole, with or without high mass ligations, may injure the internal as well as the external branch of the superior laryngeal nerve (fig. 2).

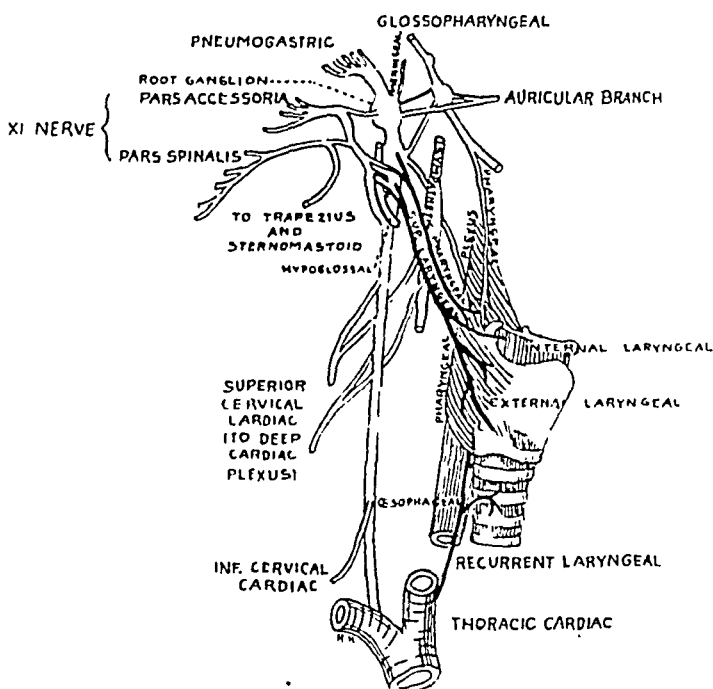


Fig. 1.—Nerve trunks that may be involved following ligations and the removal of the superior thyroid pole, resulting in: (1) complete or partial loss of the voice; (2) laryngeal obstructive dyspnea; (3) aspiration of ingested fluids into the bronchi; (4) loss of sensation to the mucosa of the upper sphincteric larynx; (5) the thyromandibular reflex; (6) the vagopinna reflex; (7) paralysis of the soft palate, and (8) referred pain throughout the somatic distribution of the first four cervical nerves.

The upper extremity of the superior pole of the thyroid, in a normal condition, usually lies opposite the upper portion of the lateral surface of the thyroid cartilage. Not infrequently, and particularly when hypertrophied, it lies opposed to the thyrohyoid membrane (fig. 2), and I have found enlarged poles lying against and even above the hyoid bone. In short-necked persons any sized gland may lie relatively much higher. Most anatomic textbooks describe the upper pole of a normal gland in a lower position than it is generally found in the living sub-

ject, owing, perhaps, to cadaveric contraction. The upper extremity of the pole generally lies higher than the gland's first point of contact with the superior thyroid artery, which is on its anterior surface. In endeavoring to ligate the vessels before they reach the upper level of the superior pole of an enlarged gland with a high superior pole, the ligature or clamp must therefore lie close to or opposite the thyrohyoid membrane. In such ligations, particularly with the high lying or goitrous superior pole, the internal as well as the external branches of the superior laryngeal nerve may be involved (fig. 2).

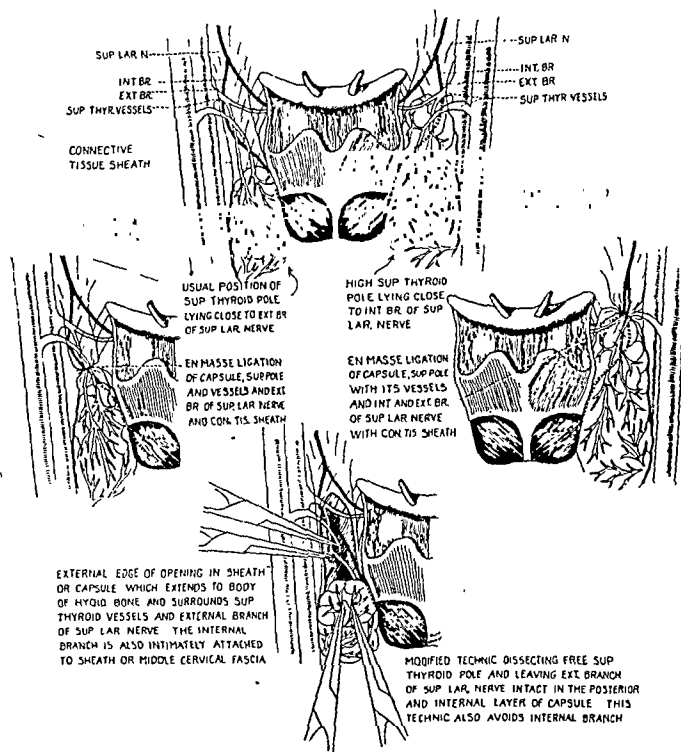


Fig. 2.—Upper, moderately high and high positions of the superior poles. Right, ligature involving vessels of the superior pole and the external branch of the superior laryngeal nerve. Left, ligature involving vessels of the superior pole and both external and internal branches of the superior laryngeal nerve. Lower, new technic which dissects the superior pole from behind the thyroid sheath, leaving both branches of the superior laryngeal nerve intact.

Not infrequently, there is a posterior branch of the superior thyroid artery which lies along the posterior border of the superior pole, and often within a centimeter of the upper extremity of the inferior laryngeal nerve just before it passes beneath the lower borders of the inferior constricting muscle of the pharynx and the thyroid cartilage. In clamping or ligating the posterior branch of the superior thyroid artery near the inferior border of the thyroid cartilage, particularly while pulling the pole downward and across the trachea, the recurrent laryngeal nerve

may be injured (fig. 4). Occasionally, a high lying inferior thyroid artery approaches the gland along the lateral surface of the superior pole, within a centimeter or two of the inferior laryngeal nerve, which may be included during an attempt to ligate the vessel in this vicinity (Fig. 4). It is therefore possible to injure both branches of the superior laryngeal nerve and the upper portion of the inferior laryngeal nerve in the production of hemostasis of the superior pole.

Most anatomic textbooks infer that the superior laryngeal nerve supplies sensation to the mucosa of the larynx and supplies motor

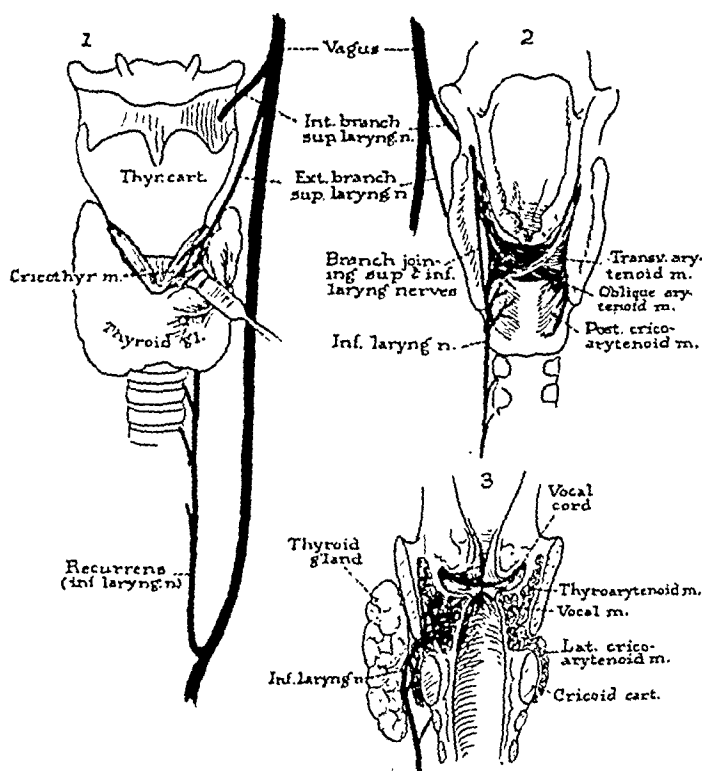


Fig. 3.—Laryngeal branches of the vagus nerve, which prove the tenth cranial nerve to be a mixture of voluntary and involuntary motor and sensory, as well as sympathetic and parasympathetic, fibers. Note in 2 a branch from the superior laryngeal supplying motor fibers to the adductor or interarytenoid muscle.

activity to only one muscle, the cricothyroid. The recent anatomic contributions by Berlin and Lahey,³ Fowler and Hanson,¹ Dilworth,⁴ New,⁵ Mullin⁶ and Nordland⁷ not only are instructive but further prove that the interarytenoid muscles, adductors of the posterior ends of the vocal cords, frequently receive innervation from the internal

3. Berlin and Lehey: *Surg., Gynec. & Obst.* **49**:102 (Oct.) 1929.

4. Dilworth, T. F. M.: *J. Anat.* **56**:48, 1921-1922.

5. New, G. B.: *Ann. Clin. Med.* **1**:262, 1923.

6. Mullin, W. D.: *Ann. Otol. Rhin. & Laryng.* **37**:627, 1928.

7. Nordland, Martin: *Surg., Gynec. & Obst.* **51**:449 (Oct.) 1930.

branch of the superior laryngeal nerve. Vegus⁸ also stated that the interarytenoid muscles in some instances receive branches from the internal branch of the superior laryngeal nerve, that the recurrent laryngeal nerve subserves sensation up to the level of the vocal cords, and that above this, sensation is from the internal branch of the superior laryngeal nerve.

I found in one instance, during the dissection of three larynges, that a twig from the internal branch of the superior laryngeal nerve extended to the interarytenoid muscle, the principal adductor of the posterior end of the vocal cord (fig. 3). When the nerve to this muscle, which may come from either the inferior or superior laryngeal nerve, is injured, adduction of the cords is about 50 per cent absent, and a marked change

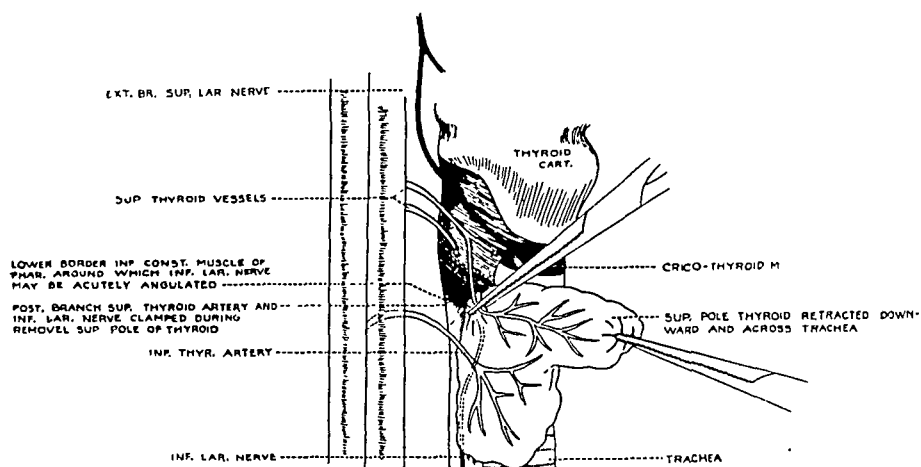


Fig. 4.—Note positions of the inferior laryngeal nerves and the posterior branch of the superior thyroid artery and how both may be crushed in hemostasis of this vessel.

in voice occurs, sometimes a total aphonia. In addition, there may be a loss of the sphincteric action of the upper part of the larynx which occasionally allows fluids to run through into the bronchi during the act of swallowing. This may also happen when the inferior pharyngeal constrictor muscle is paralyzed by injury to either the superior or inferior laryngeal nerve. This muscle elevates the larynx, sliding the glottis upward beneath the epiglottis during deglutition. The internal branch of the superior laryngeal nerve supplies sensation to at least the upper part of the larynx. When this nerve is involved in ligations of the upper pole, not only is anesthesia of the upper larynx produced but in addition there often occur: (1) interarytenoid or adductor paralysis with aphonia, (2) loss of upper laryngeal sphincteric action, (3) the

8. Vegus, V. E.: *The Mechanism of the Larynx*, London, William Heinemann, Ltd., 1929, p. 463.

thyromandibular reflex and (4) the vagopinna reflex. When anesthesia of the mucosa of the upper larynx occurs, the patient tolerates a pool of saliva resting on the vocal cords without coughing, and talks in a smothered tone as if the voice were coming through a mouth full of fluid. With this complication, there also may occur, as previously stated, an aspiration of fluids into the trachea or bronchi during the act of swallowing. The normal sensory nerve supply to the mucous membrane of the upper half of the larynx is an extremely important protective mechanism, producing, when irritated, a sphincteric action of the larynx above the vocal cords through contractions of the inter-arytenoid, thyro-arytenoid and lateral crico-arytenoid muscles, which are supplied by the superior and inferior laryngeal nerves.

The inferior laryngeal nerve, in passing upward, is closely attached to the posterior and relatively thinner border of the superior pole by interparenchymatous thyroid connective tissue, which is not the pretracheal fascia. This attachment is sometimes so firm that when the superior pole is pulled downward and across the trachea, it retains such a firm hold that the nerve not only becomes sharply kinked around the inferior borders of the inferior pharyngeal constrictor muscle and thyroid cartilage but may be detached from its terminal muscle beds (fig. 4). In addition, as previously stated, it may be so elevated from its posterior position that a hemostat could easily involve it when a branch of the superior or inferior arteries needs clamping along the posterior edge of the superior thyroid pole (fig. 4). I have found repeatedly, as Fowler and Hanson reported, that the inferior laryngeal nerve is not held attached to the posterior border of the thyroid gland by the pretracheal fascia. Judd⁹ stated, in 1921, that he was under the impression that the inferior laryngeal nerve was frequently injured near its entrance into the larynx.

THE THYROMANDIBULAR REFLEX

The thyroid gland is supplied by sympathetic nerves which reach the gland as plexuses along the superior and inferior thyroid arteries from the superior and middle sympathetic cervical ganglions respectively. Branches, probably from the superior laryngeal nerve, are often seen to accompany the superior polar vessels along the anterior surface of the gland. When the superior thyroid vessels are ligated, under local anesthesia, the patient frequently complains of pain in the lower molar teeth on the corresponding side. Much more rarely pain is experienced along the lateral border of the tongue. The anatomic pathways of this reflex have, as far as I could determine, not been described. In considering the rôle of the autonomic neurons in visceral afferent and

9. Judd, E. S.: *Ann. Surg.* **73**:321, 1921.

effluent stimuli, it must be kept in mind that one preganglionic neuron enters into synaptic reactions with numerous postganglionic neurons, producing a wide radiation of efferent reactions from a single afferent stimulation. Every sympathetic ganglion receives fibers from more than one reflex arch in the spinal cord, and splanchnic or visceral sympathetic irritation may be relayed to somatic or peripheral sensory zones and vice versa.

The superior cervical sympathetic ganglion which sends fibers along the superior thyroid artery to the thyroid gland is connected, through gray rami communicantes, to the first four cervical spinal nerves. The sensory root of the trigeminal nerve is a long columnar neuropil known as the substantia gelatinosa, which extends downward through the posterior part of the medulla oblongata and upper spinal cord to the level of the second spinal nerve. It is the largest and most sensitive of all sensory roots and is attached intimately to the posterior or sensory horn of gray matter of the cord as low as the second spinal nerve. The

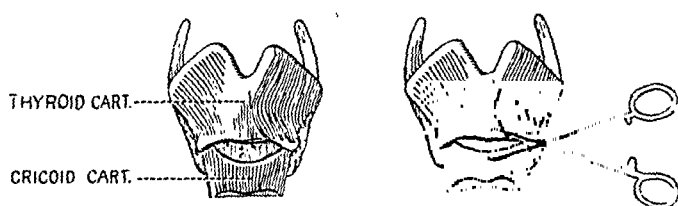


Fig. 5.—Approximating the anterior edges of the thyroid and cricoid cartilages raises the tone of the vocal cords; separating them, as in paralysis of the crico-thyroid muscles, lowers the tone of the vocal cords. It may be possible to raise or lower the tone of the singing voice by a similar technic.

pathway of the thyromandibular, splanchnosomatic, sensory reflex quite likely originates on the sympathetic plexus of the superior thyroid artery, passing to the superior cervical sympathetic ganglion, from there to the first or second cervical posterior root ganglion by way of gray rami communicantes and from there to the posterior or sensory horn of the spinal cord, spilling or synapsing onto the substantia gelatinosa which sends somatic sensory impulses along the mandibular nerve to the lower molar teeth. Why it does not send sensory impulses through the ophthalmic and maxillary branches of the trigeminal nerve is a deeper physiologic and anatomic mystery. Therefore, when trauma to the superior thyroid artery produces pain in the lower molar teeth, one has a compounded nerve reflex which probably originates in a sympathetic arterial nerve plexus, passes through a sympathetic ganglion to the ganglion of a sensory root of a spinal nerve and then, instead of only an immediate somatic zone registration supplied by the usually correlating upper cervical nerves, a portion of the impulse jumps to the most highly sensitive sensory root of another (cranial) sensory nerve

and registers in the somatic or peripheral zone of the inframandibular branch of the trigeminal nerve. The superior cervical sympathetic ganglion is also connected with the petrosal ganglion of the glossopharyngeal nerve, to the ganglion of the root and trunk of the vagus, to the hypoglossal nerve and to the pharyngeal plexus. Keeping these connections in mind in addition to the connections with four upper sensory cervical spinal nerves, it may be better understood why patients complained of so much pain during superior polar ligations of exophthalmic goiters as frequently practiced previous to the era of preoperative preparation with iodine. The ligated poles sent impulses to sensory zones well above and below the locally anesthetized area.

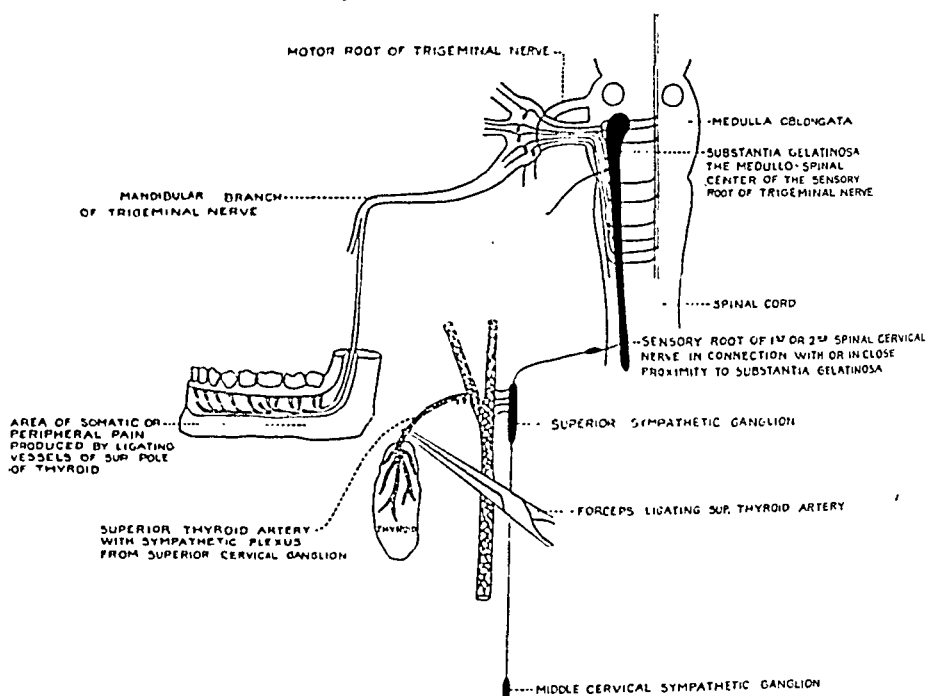


Fig. 6.—Diagram illustrating the possible reflex when the superior pole of the thyroid is ligated or clamped: the thyromandibular reflex.

THE VAGOPINNA REFLEX

When the superior laryngeal nerve is ligated, clamped or given an injection, particularly the internal branch, an occasional patient complains of pain in the external rim of the auditory canal and in the lower internal portion of the pinna. The reverse of this is true when the auditory canal is irritated, which often produces laryngeal irritation and coughing. The pathway of this first reflex originates in the superior laryngeal nerve, passing to the ganglion of the trunk of the vagus and from here out through Arnold's nerve which is an auriculovagus sensory somatic branch, the peripheral distribution of which terminates in anterior and posterior branches on the external ear or auricle.

The posterior branch of Arnold's nerve, which supplies the skin over the lower and internal surface of the pinna, is known as "alderman's nerve," owing to the treatment that the old governors of London accepted from their servants, who stroked the posterior surface of the external ears or pinnae of their masters with acrid and cooling solutions, alleviating in many instances the feeling of an overfilled stomach which these well satiated gentlemen contracted numerous times during a banquet of long duration. Stimulating the somatic sensory terminations of the posterior peripheral branch of Arnold's nerve sent a stimulus to the ganglion of the trunk of the vagus, which, in turn, promoted a much desired but then much more poorly understood peristalsis.¹⁰

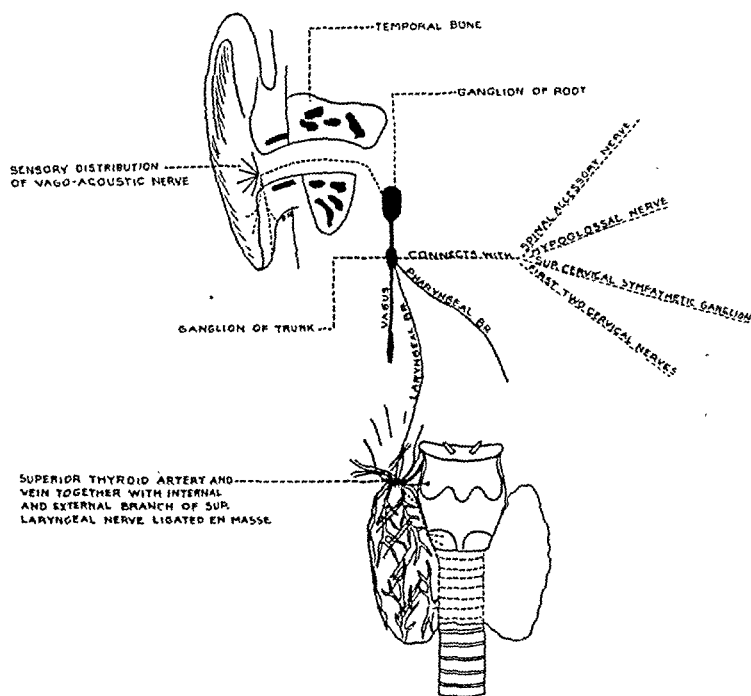


Fig. 7.—The vagopinna reflex.

PARALYSIS OF THE SOFT PALATE

Not infrequently patients who have had bilateral ligations of the superior thyroid vessels, with or without resections, complain for twenty-four to forty-eight hours of fluids coming through their nostrils from the pharynx during the act of swallowing. Normally this is prevented by the soft palate's elevating muscles, the levator palati, which are supplied through the pharyngeal plexus by the accessory vagus nerve, which connects the plexus with the ganglion of the trunk of the vagus. In what manner or by what nerve paths the motor nerves supplying the levator palati muscles are interfered with following superior polar

10. Poynter, W. M.: Personal communication to the author.

vessel ligations is not understood. The superior cervical sympathetic ganglion and the superior laryngeal nerve may be involved, or a direct injury to the pharyngeal plexus is possible. Since this paralysis lasts for a day or two only, a reflex pathway is indicated.

The inferior constrictor muscle of the pharynx, one of an important group of muscles in swallowing and the principal elevator of the larynx, is innervated sometimes by the superior laryngeal nerve. If this muscle is involved, the cooperative muscular contractions of the constrictor may be absent during swallowing, resulting in a tardy or absent contraction of the elevating muscles of the soft palate, which may not of necessity be paralyzed.

OPERATIVE PROCEDURES

There has been no particular technic advocated or adopted for the liberation and resection of the superior pole of the goitrous thyroid. Kocher¹¹ may have been the first surgeon to advise a consideration of the superior laryngeal nerve. In August, 1928, before a meeting of the state societies of Wyoming, Montana and Idaho, held in Yellowstone Park, I reported my experience with the superior laryngeal nerve, which had extended back over a period of eight years. I reported also a technic for exposing the superior pole and vessels which avoided the branches of the superior laryngeal nerve.

In 1920, during an attempt to develop a new technic for bilateral resections of the goitrous thyroid and with a patient under local peripheral sensory nerve block, I exposed as a preliminary step both superior poles of a large goiter, which lay opposed to the thyrohyoid membrane. After placing a ligature around the upper end of one superior pole and its sheath, I noticed a moderate lowering of tone in the patient's voice as she complained of referred pain in the lower molar teeth on the corresponding side as well as pain in the pinna of the external ear. When a second ligature was placed around the upper end of the other superior pole, the patient experienced only the thyromandibular reflex, but could not speak, owing to an aphonia of about 90 per cent which lasted for four months. During this time, the posterior ends of each vocal cord failed to approach the midline due to an interarytenoid adductor paralysis, which in some instances persists for only four to six months. Since this experience, whenever a patient is under local anesthesia only, I have tested the voice and inquired about referred somatic pains as each polar set of vessels is ligated. These referred pains in the lower teeth have been noticed by other surgeons, but have not been dwelt on in the literature, to any extent at least. With the development of the technic to be described, the occurrence of

11. Kocher, quoted by Nordland (footnote 7).

changes in the tone of voice and referred pains has markedly decreased. In advanced cases of toxic thyroidism, when a psychic block is desirable through the use of light gas analgesia, a voice and referred somatic pain test during resection of the superior pole cannot be made. Since a psychic block in addition to a local peripheral sensory nerve block is practiced by many of the most experienced surgeons in this field, a technic is desirable that will avoid the branches of the superior laryngeal nerve, as well as the inferior, under any type of anesthesia.

During an operation under local anesthesia or after the patient is allowed to awaken from a psychic block produced by gas, a higher pitch to the voice may be obtained by approximating the cricoid and thyroid cartilages with a towel clip (fig. 5). In one case of bilateral cricothyroid paralysis, with a marked lowering of the singing voice, I wired the cricoid up beneath the lower border of the thyroid cartilage in an attempt to restore the patients voice to a higher tone (fig. 8). This

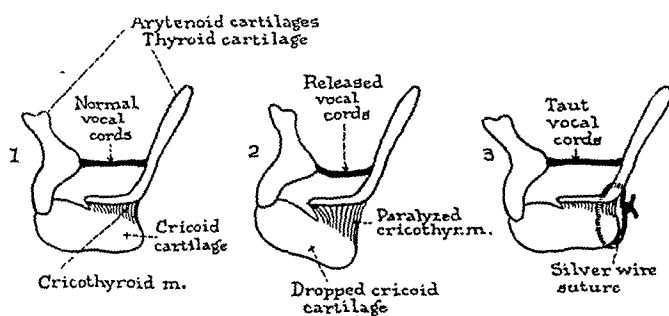


Fig. 8.—Lateral view of the thyroid and cricoid cartilages, including the vocal cords and cricothyroid muscles. In 2, note the relaxation of the vocal cords when the cricothyroid muscle is paralyzed by injury to the external branch of the superior laryngeal nerve.

resulted in raising her voice to an undesirably high pitch which persisted for over six months. About one year after removal of the wire, the tone was lowered, but its previous clarity never completely returned. In singers a resection of a goitrous thyroid must be given due consideration relative to the superior as well as the inferior laryngeal nerve. There is a possibility of changing singing tones to a higher or lower pitch by elevating with a suture or depressing the cricoid cartilage through a paralysis of the cricothyroid muscles. Undoubtedly, many of the postoperative husky and lower voices result from injury to only the external branches of the superior laryngeal nerves.

TECHNIC OF SUPERIOR POLE RESECTIONS

The modified Kocher flap is used, which I described in *The Journal of the American Medical Association*.¹² This gives the greatest mobil-

12. Roeder, C. A.: Thyroidectomy, *J. A. M. A.* **79**:2066 (Dec. 16) 1922.

ity of the ribbon muscles without a transverse section. When it is necessary to cross-section these muscles, the sternomastoid muscle is first liberated by Lahey's method, and a modified Masten clamp (fig. 9) is then applied, which, after severing the muscles, gives ample exposure of the superior pole without the use of sharp pointed retractors or forceps. The superior thyroid vessels on the anterior surface of the superior poles are individually caught and ligated after the sheath has been split longitudinally (fig. 1). Each pole is then lifted from its bed in this sheath of pretracheal fascia, which leaves the superior laryngeal branches of the vagus and all adjacent nerve trunks uninjured. When a posterior branch of the superior thyroid artery is present, it is ligated well away from the inferior laryngeal nerve as it approaches the inferior borders of the inferior pharyngeal constrictor muscle and the

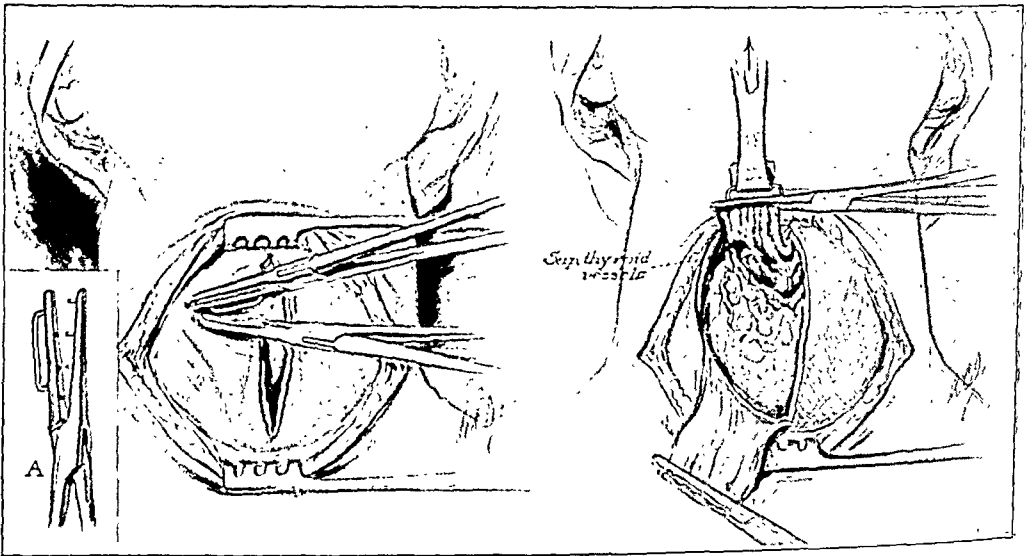


Fig. 9.—Modified Masten clamp for cross-sectioning ribbon muscles. Note the loop into which a retractor is placed, preventing slipping and tearing of the muscles. In most instances transverse section of ribbon muscles is not necessary, when the flap is made according to a technic described in 1922 (Roeder, C. A.: Thyroid-ectomy, *J. A. M. A.* **79**:2066 [Dec. 16] 1922).

thyroid cartilage, a technic which may leave occasionally a portion of the posterior edge of the superior pole over the upper end of the inferior laryngeal nerve. Care is taken not to pull the pole too far downward and across the trachea in order to avoid stretching or sharply angulating the upper extralaryngeal end of the inferior laryngeal nerve (fig. 4). Whenever a patient who is under only segmental or local anesthesia complains of pain in the somatic distribution of Arnold's nerve during ligation of the superior thyroid vessels, it is a positive warning that the superior laryngeal nerve is involved. When this reflex does not occur, however, it does not indicate that this nerve is not involved. From traction on the superior poles downward and across the trachea after

liberation from their sheaths, the patient's voice may suddenly change or disappear. If traction has not been too severe, the voice returns immediately. This is an indication of trauma to the inferior laryngeal nerve where it lies attached to the posterior border of the superior pole, or to sharp angulation of the nerve around the inferior border of the inferior pharyngeal constrictor muscle (fig. 4). It must be kept in mind that one or both inferior laryngeal nerves may be injured by traction on the superior poles, which may account for the unexplained cases of paralysis of the vocal cord following an operation that did not clamp or ligate the nerves. Traction downward on the superior pole before its sheath is liberated may injure the internal branch of the superior laryngeal nerve, producing an adductor paralysis (fig. 1).

CONCLUSIONS

During the removal of the superior pole of a goitrous thyroid, the following significant complications may occur:

- (1) Injuries to the inferior and superior laryngeal branches of the vagus, producing:
 - (a) Partial or complete loss of voice
 - (b) Obstruction to inspiration
 - (c) Aspiration of ingested fluids into the bronchi
 - (d) Loss of sensation to the mucosa of the larynx
 - (e) Referred pain to the lower portion of the pinna through the "vago-pinna reflex"
- (2) Referred pain to the mandibular teeth through the "thyromandibular reflex"
- (3) Paralysis of the soft palate
- (4) Referred somatic pain through any or all of the first four cervical spinal sensory nerves
- (5) Hemorrhage from the superior thyroid vessels
- (6) Injury to or removal of parathyroid glandules

THE RÔLE OF PERIOSTEUM IN THE HEALING OF FRACTURES

AN EXPERIMENTAL STUDY *

KEENE O. HALDEMAN, M.D.

SAN FRANCISCO

The rôle played by the various components of bone in the healing of fractures has been the subject of many researches since the work of Duhamel¹ in 1741. It is, of course, one of great practical importance as well as of theoretical interest. Because of the volume of the literature and the variety of opinions held, a classification of the theories of bone repair is quoted from Bancroft,² who has summarized this subject as follows:

1. The periosteal theory presupposes that the periosteum and endosteum are definite organs for bone formation and repair, and that the bone cells arise from them and from no other source.

2. The osteoblastic theory may be divided into two subtitles.

Type A. This assumes that in bone repair following injury bone cells are liberated from their lacunae and that they reproduce and form new bone.

Type B. This assumes that following injury wandering connective tissue cells, fibroblasts, are drawn into the area of trauma. Owing to the stimulus of the repair, they are transformed into bone producing cells and then become specific cells.

3. The extracellular deposition of calcium salts theory assumes that there is no definite bone producing cell; that following injury, possibly by positive chemotaxis, calcium salts in the proportions usually found in bone are deposited in the extracellular framework of connective tissue and that the connective tissue cell then becomes a bone cell by functional adaptation.

A more comprehensive view of this whole problem may be obtained from an inspection of figure 1. As can be seen, the controversy regarding the osteogenic property of periosteum is not a recent one. The first champion of periosteum as a bone-forming tissue was Duhamel.¹ He employed the method of feeding madder, which had been discovered five years before by Belchier.¹ The bones of animals fed on this alizarin-containing plant became red, because of the elective

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* From the Department of Orthopedic Surgery of the University of California Medical School.

* Read before the Section on Industrial Medicine and Surgery, at the Sixtieth Annual Session of the California Medical Association, San Francisco, April 28, 1931.

1. Quoted by Keith: Brit. J. Surg. 5:685, 1918.

2. Bancroft, F. W.: Bone Repair Following Injury and Infection, Arch. Surg. 5:646 (Nov.) 1922.

staining of the newly formed bone. Duhamel observed that the periosteum in the neighborhood of a fracture became greatly swollen, and was chiefly responsible for the formation of the repairing callus.

Opposed to the theories of Duhamel was John Hunter,¹ who was greatly influenced by the teachings of Haller. Haller and Hunter believed that the periosteum was merely a vascular covering that served for the nourishment of the bone. They were convinced that only the arteries had the ability to form bone. Hunter brought out the fact that two processes were at work together in the growth of bone, namely, deposition and absorption.

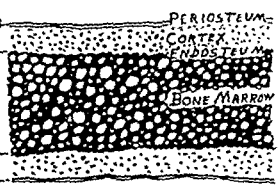
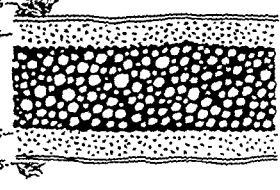
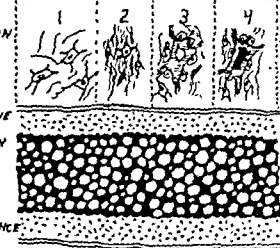
TITLE	ADVOCATES AND YEAR	OSTEOGENIC ELEMENTS	STRUCTURE OF BONE (DIAGRAMMATIC)
PERIOSTEAL	DUHAMEL 1741 SYME 1835 OLLIER 1867 AXHAUSEN 1898 MAYER AND WEHNER 1914 PHEMISTER 1914 BERG AND THALHIMER 1918 RÖHDE 1925 BLAISDELL AND COWAN 1926 MOCK 1928 HAM 1930	PERIOSTEUM— ENDOSTEUM— ENDOSTEUM— PERIOSTEUM—	
OSTEOBLASTIC 1. BONE CELLS 2. FIBROBLASTS	GOODSIR 1841 MACEWEN 1912 BROWN AND BROWN 1913 DAVIS AND HUNNICUTT 1915 GALLIE AND ROBERTSON 1919 KEITH 1927 JAFFE 1929	FIBROBLASTS— BONE CELLS— BONE CELLS— FIBROBLASTS—	
EXTRA-CELLULAR DEPOSITION OF CALCIUM SALTS	BANCROFT 1922 LERICHE AND FOLICARD 1928 MURRAY 1930	PHASES OF OSSIFICATION (LERICHE AND FOLICARD) 1. EDEMA OF CONNECTIVE TISSUE 2. MULTIPLICATION OF FIBRILS 3. DEPOSITION OF PRE-OSSIOUS SUBSTANCE 4. CALCIFICATION	

Fig. 1.—Diagram to illustrate the theories of bone repair.

To review all the experimental work that has been cited for or against the osteogenic function of periosteum would exceed the bounds of the present paper. It may suffice to enumerate the workers who have advocated each of the theories of the formation of bone. Since Duhamel, the primary rôle in this process has been assigned to the periosteum by Syme,³ 1835; Flourens,⁴ 1842; Ollier,⁴ 1867; Axhausen,⁵

3. Quoted by Keith: Brit. J. Surg. 6:19, 1918.

4. Quoted by Keith (footnote 3, p. 160).

5. Axhausen, G.: Die histologischen und klinischen Gesetze der freien Osteoplastik auf Grund von Thierversuchen, Arch. f. klin. Chir. 88:23, 1909.

1909; Haas,⁶ 1913; Mayer and Wehner,⁷ 1914; Phemister,⁸ 1914; Berg and Thalhimer,⁹ 1918; Rohde,¹⁰ 1925; Blaisdell and Cowan,¹¹ 1926; Mock,¹² 1928, and Ham,¹³ 1930.

Following Haller and Hunter in a denial of the osteogenic function of periosteum, Goodsir³ in 1845 first advanced the theory that bone cells ("corpuscles") had the power to form new bone. The next advocate of the osteoblastic theory was Macewen.¹⁴ In 1912, he repeated many of the experiments of Ollier, obtaining different results, probably to be explained on the assumption that Macewen included less tissue in his removal of periosteum. Whereas Ollier had obtained a growth of new bone from periosteal transplants, Macewen was unable to find newly formed bone in such grafts, and noted the growth of bone from the surface of the cortex that had been denuded of periosteum.

Later supporters of the osteoblastic theory of bone repair include Brown and Brown,¹⁵ 1913; Davis and Hunnicutt,¹⁶ 1915; Gallie and Robertson,¹⁷ 1919; Keith,¹⁸ 1927, and Jaffe,¹⁹ 1929. The term "osteoblastic theory" covers numerous rather divergent views of the growth of bone. Macewen believed that the bone cell of the cortex was the

6. Haas, S. L.: Regeneration of Bone from Periosteum, *Surg., Gynec. & Obst.* **17**:164, 1913.

7. Mayer, L., and Wehner, E.: An Experimental Study of Osteogenesis, *Am. J. Orthop. Surg.* **12**:213, 1914.

8. Phemister, D. B.: The Fate of Transplanted Bone and Regenerative Power of Its Various Constituents, *Surg., Gynec. & Obst.* **19**:303, 1914.

9. Berg, A. A., and Thalhimer, W.: Regeneration of Bone, *Ann. Surg.* **67**:331, 1918.

10. Rohde, C.: Does Bone Form from Osteoblasts or from a Metaplasia of the Surrounding Connective Tissue? *Surg., Gynec. & Obst.* **41**:740, 1925.

11. Blaisdell, F. E., and Cowan, J. F.: Healing of Simple Fractures: An Experimental Study, *Arch. Surg.* **12**:619 (March) 1926.

12. Mock, H. E.: Periosteal Transplants in the Repair of Delayed Union, Ununited Fractures, and Loss of Bone Substance, *Surg., Gynec. & Obst.* **46**:641, 1928.

13. Ham, A. W.: A Histological Study of the Early Phases of Bone Repair, *J. Bone & Joint Surg.* **12**:827, 1930.

14. Macewen, W.: *The Growth of Bone*, Glasgow, James Maclehose & Sons, 1912.

15. Brown, W. L., and Brown, C. P.: Preliminary Report on Experimental Bone and Periosteal Transplantation, *Surg., Gynec. & Obst.* **17**:681, 1913.

16. Davis, J. S., and Hunnicutt, J. A.: The Osteogenic Power of Periosteum: With a Note on Bone Transplantation, *Ann. Surg.* **61**:672, 1915.

17. Gallie, W. E., and Robertson, D. E.: The Repair of Bone, *Brit. J. Surg.* **7**:211, 1919.

18. Keith, A.: Concerning the Origin and Nature of Osteoblasts, *Proc. Roy. Soc. Med. (Sect. Surg.)* **21**:301, 1927.

19. Jaffe, H. L.: The Structure of Bone: With Particular Reference to Its Fibrillar Nature and the Relation of Function to Internal Architecture, *Arch. Surg.* **19**:24 (July) 1929.

active agent in the deposition of calcium salts. Hey Groves²⁰ pointed out that osteoblasts develop most rapidly in the haversian canals of a bone graft. In discussing the formation of bone in laparotomy wounds, Keith held that osteoblasts develop from the buds of capillary endothelium which invade the scar tissue.

The theory of the extracellular deposition of calcium salts, as described, is favored by Bancroft. Murray²¹ has reported work that supports this theory. A recent book by Leriche and Policard²² is devoted chiefly to the support of the thesis that bone is formed by the impregnation with calcium salts of an edematous connective tissue. This connective tissue first reverts to an embryonic state and then undergoes what these authors term a preosseous infiltration. Leriche and Policard expressed the belief that the chief function of the periosteum is to limit bone growth, although they conceded that it is a connective tissue medium favorable for the development of bone. In regard to the osteoblasts, these authors regarded them as osteolytic elements that represent reactionary attempts of the connective tissue cells against the preosseous transformation.

That the periosteum may hinder as well as assist the union of fractures had been pointed out by Cowan.²³ In a microscopic study of experimental fractures in dogs and kittens, this worker found that the ends of the fragments were sometimes prevented from fusing and reestablishing vascular communication by the ingrowth of dense avascular fibrous tissue from the periosteum. When a hole was drilled in the patella, it became plugged with fibrous tissue that apparently was continuous with the periosteum.

From a clinical standpoint, the question as to the osteogenic function of the periosteum is of importance chiefly in the healing of bone following fractures, and in the behavior of bone grafts. If the periosteum forms bone, every effort should be made to conserve it near fractures and on bone grafts. To determine the value of periosteum in the vicinity of fractures, a series of experiments was done on eight rabbits and two dogs.

METHODS

In general, the method followed was the production of a fracture or defect in each of two comparable bones of the same animal, with a different treatment of the periosteum on the right and left sides. The two radii in rabbits or the two fibulae in dogs usually were attacked. X-ray pictures of the operative sites were

20. Hey Groves, E. W.: *Methods and Results of Transplantation of Bone in the Repair of Defects Caused by Injury or Disease*, *Brit. J. Surg.* **5**:185, 1917.

21. Murray, C. R.: *The Repair of Fractures*, *Minnesota Med.* **13**:137, 1930.

22. Leriche, R., and Policard, A.: *The Normal and Pathological Physiology of Bone*, St. Louis, C. V. Mosby Company, 1928.

23. Cowan, J. F.: *Non-Union of Fractures: An Experimental and Clinical Study*, *Ann. Surg.* **88**:749, 1928.

made immediately following the operation and at weekly intervals thereafter until union occurred or the fact of nonunion was established clearly. The animals were then killed, and microscopic studies were made of the sites of operation. Sodium amytal, given intraperitoneally in dosages of 0.060 Gm. per kilogram of body weight, provided the anesthesia in all operations. Sterile technic was used, and incisions were closed with black silk and covered with dry dressings. No splints were necessary as the intact ulna or tibia prevented undue movement of the fractured bone. In no case did infection of the wound occur.

The experiments fall into four groups; the protocol of a typical experiment of each group is given.

Group A.—Saw cut in each radius, stripping periosteum on the left.

Rabbit 11 was a young adult weighing 2.3 Kg. The right radius was divided with a saw at the junction of its middle and distal thirds. The periosteum was incised transversely at the level of the saw cut, but was not otherwise disturbed. A similar saw fracture was produced near the middle of the left radius, and the periosteum was scraped from each fragment with a knife and periosteal elevator for a distance of 1 cm. on either side of the cut. X-ray pictures of both forelegs were taken immediately after the operation and at weekly intervals for six weeks. The animal was killed forty-three days after the operation, and microscopic sections of each radius were prepared. The results of all the experiments will be discussed together.

Rabbit 15 was subjected to a similar operation and was killed fifty-eight days after the operation. Roentgen and microscopic studies were made.

Group B.—Segment removed from each radius, stripping periosteum on the left.

Rabbit 21 was a young adult weighing 2.5 Kg. A segment 0.5 cm. in length was removed with its periosteum from the middle third of each radius. The periosteum on the fragments of the right radius was not disturbed. Both fragments of the left radius were denuded of periosteum for a distance of 1 cm. from the operative defect. X-ray pictures were taken following the operation, at weekly intervals for six weeks and at eight weeks. The animal was killed fifty-eight days after the operation, and microscopic sections were made through the sites of operation. Two other experiments of the same type were performed on rabbits 12 and 14, the former being killed after one hundred and seventy-three days and the latter after sixty-five days.

Group C.—Segment removed from each radius, drawing the periosteum over the ends of the right radius.

Rabbit 52 was a young adult weighing 2.5 Kg. The right radius was exposed; its periosteum was incised transversely at the middle of the shaft and was reflected back 0.5 cm. on either side of this point. A segment of radius, 0.3 cm. in length, was removed from the middle of this denuded area, after which the reflected flaps of periosteum were drawn back over the cut ends of the radius. A segment of equal length was removed with its periosteum from the middle third of the left radius. The periosteum was pushed back on each fragment of the left radius for a distance of 0.1 cm. from the defect, so as to prevent the periosteum falling over the ends of the radius. X-ray pictures were taken immediately after the operation and after fourteen, twenty-one and twenty-six days. The animal was killed after twenty-six days, and microscopic sections were made. Similar experiments were done on rabbits 40 and 49, but in these animals the condition was allowed to progress further, namely, fifty-eight and sixty-eight days.

Group D.—Segment removed from each fibula of a dog, drawing the periosteum over the ends of the right fibula.

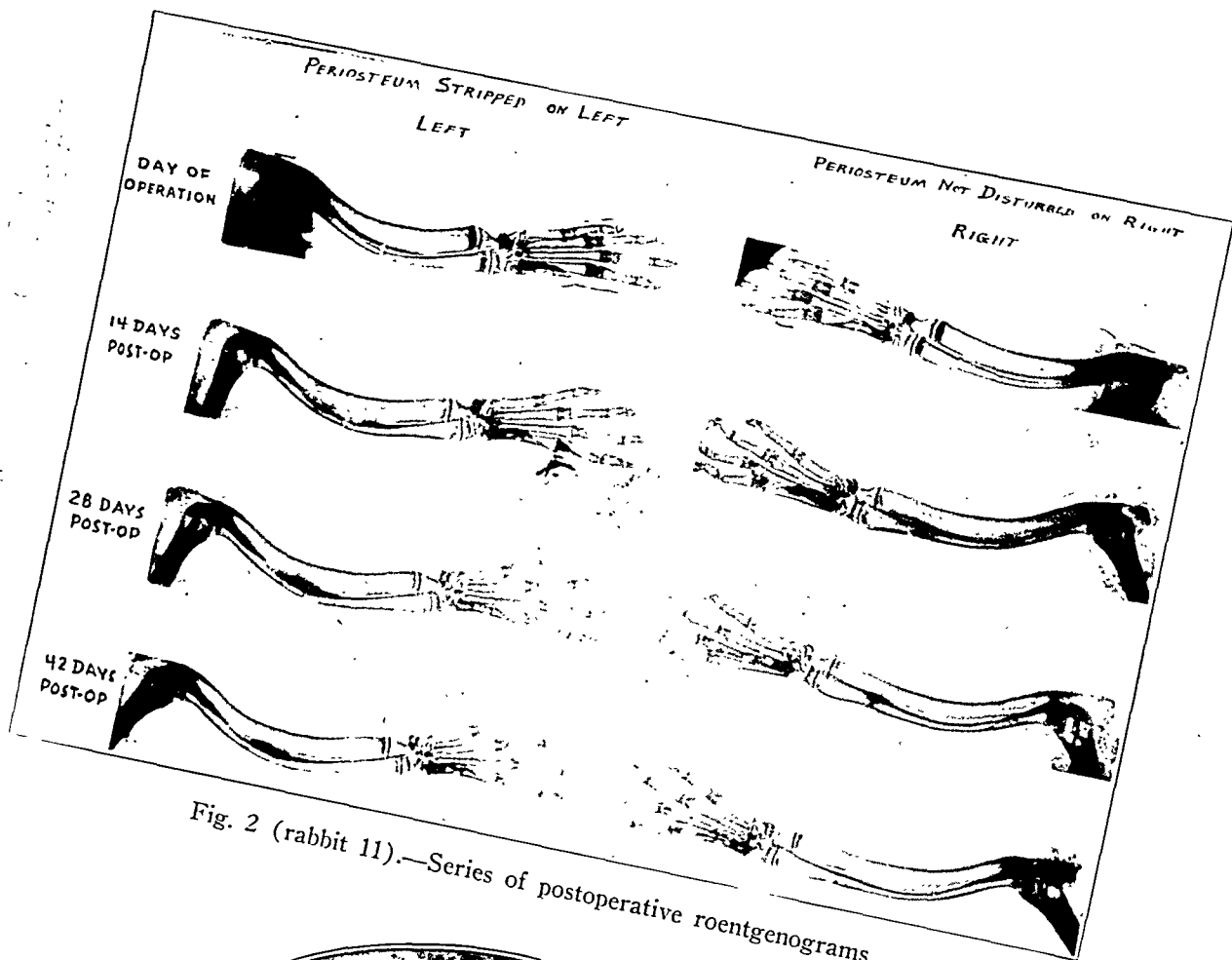


Fig. 2 (rabbit 11).—Series of postoperative roentgenograms.



Fig. 3 (rabbit 11).—Photomicrograph of left radius at the point of attachment of the periosteum.

Dog 41 was a large adult. The right fibula was exposed by a lateral incision splitting the fibers of the peroneus longus muscle. The periosteum was incised transversely at the junction of the middle and distal thirds of the fibula and was reflected to expose a segment of fibula 0.4 cm. in length, which was excised. The reflected flaps of periosteum were then drawn over the cut ends of the right fibula. The left fibula was exposed, and a segment 0.4 cm. in length was removed at the junction of its middle and distal thirds. The periosteum on the fragments of the left fibula was pushed back 0.1 cm. from the cut surface. X-ray pictures of both fibulae were taken after the operation and at intervals of four, five, seven, nine and eleven weeks. The animal was killed seventy-nine days after the operation. Gross examination showed a fibrous union of the left fibula, whereas no union had occurred in the right fibula. Microscopic sections were made. In another dog, no. 43, a similar experiment was performed, and the animal was killed after ninety-one days.

RESULTS

GROUP A.—In the two cases of this group, the right radius, with periosteum undisturbed, united in four weeks. The left radius, with periosteum stripped back from the saw cut, failed to unite across the outer cortex at the end of six weeks. The layer of cortex adjacent to the ulna united, possibly because the two bones of the rabbit's foreleg are very close together, so that the periosteum of the ulna is necessarily irritated by any operation on the radius (fig. 2). Microscopic examination of the left radius confirmed the impression given by the x-ray pictures. No newly formed bone was seen on the surface of the cortex until the point of attachment of the remaining periosteum was reached. Here subperiosteal callus could be seen (fig. 3).

GROUP B.—In the three cases comprising this group, the gap in the right radius was completely closed in one, almost closed in another and about one-half closed in the third. Microscopic section showed an active production of subperiosteal callus in each of these cases. On the contrary, the left radius, from the ends of which the periosteum had been stripped, presented no attempt at callus production in any case, as observed by roentgen examinations (fig. 4) and microscopic section (fig. 5). Each of the three cases gave the typical picture of nonunion with tapering ends of bone projecting into fibrous tissue.

GROUP C.—In the three rabbits of this group the gap in the left radius was filled with new bone in four weeks. At the end of twenty-six days the fracture in the right radius showed by x-ray pictures (fig. 6) and microscopic examination (fig. 7) the typical picture of nonunion. In the two experiments lasting fifty-eight and sixty-five days there was a partial union of the fractures in the right radius because of the production of endosteal callus, but the external portions of the cortex failed to unite.

GROUP D.—Two dogs were used. In dog 41, the x-ray pictures (fig. 8) showed a tonguelike process of new bone growing upward

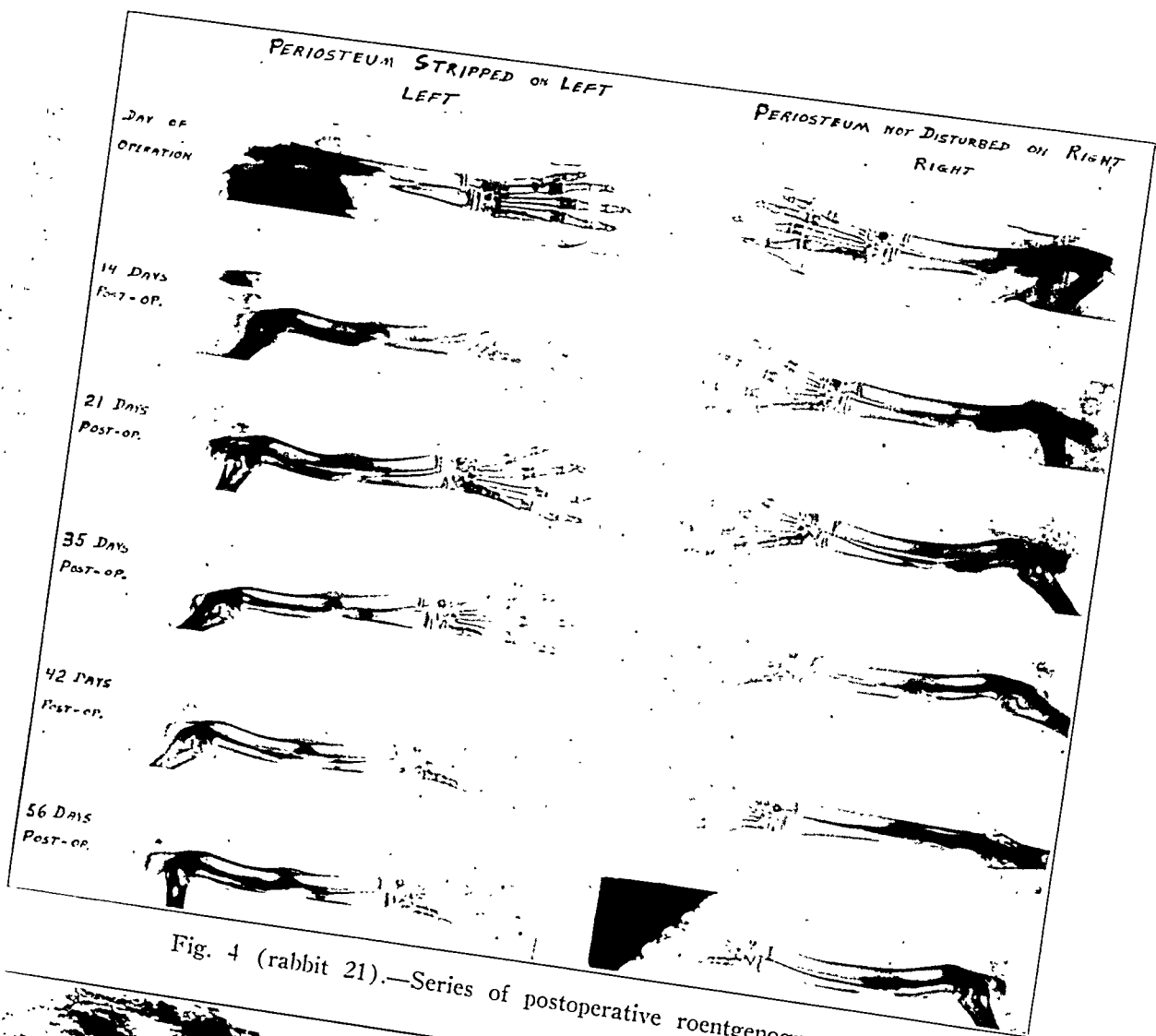


Fig. 4 (rabbit 21).—Series of postoperative roentgenograms.

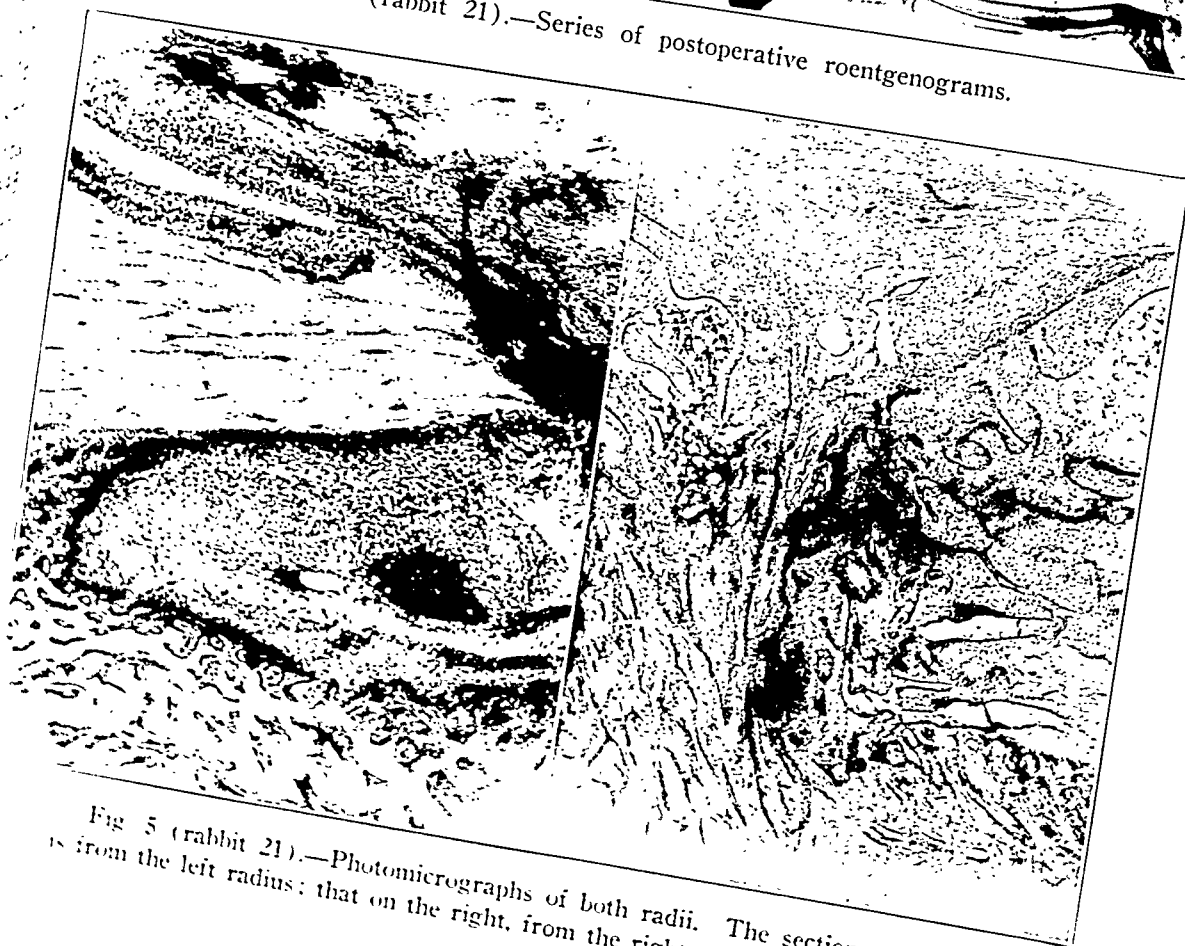
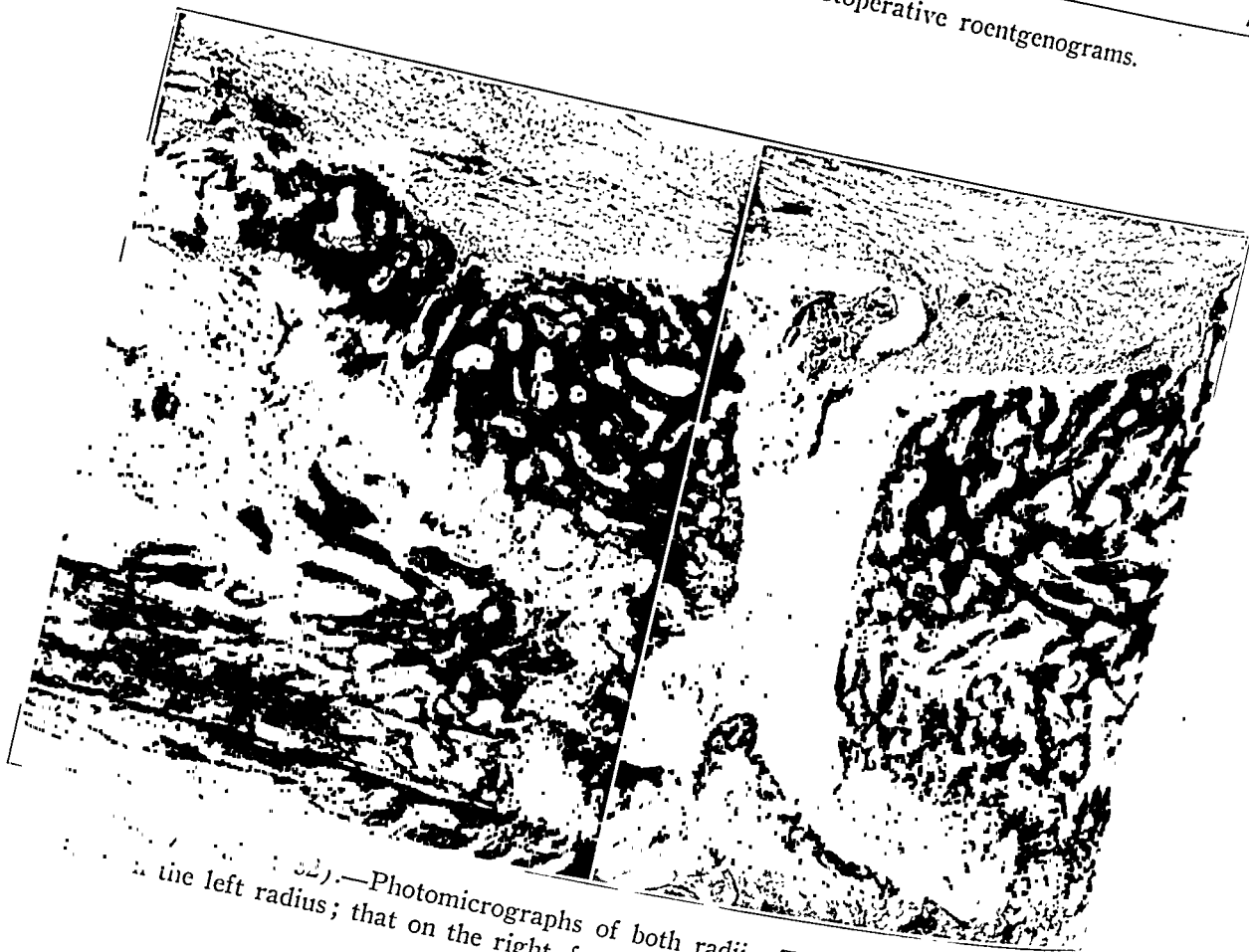
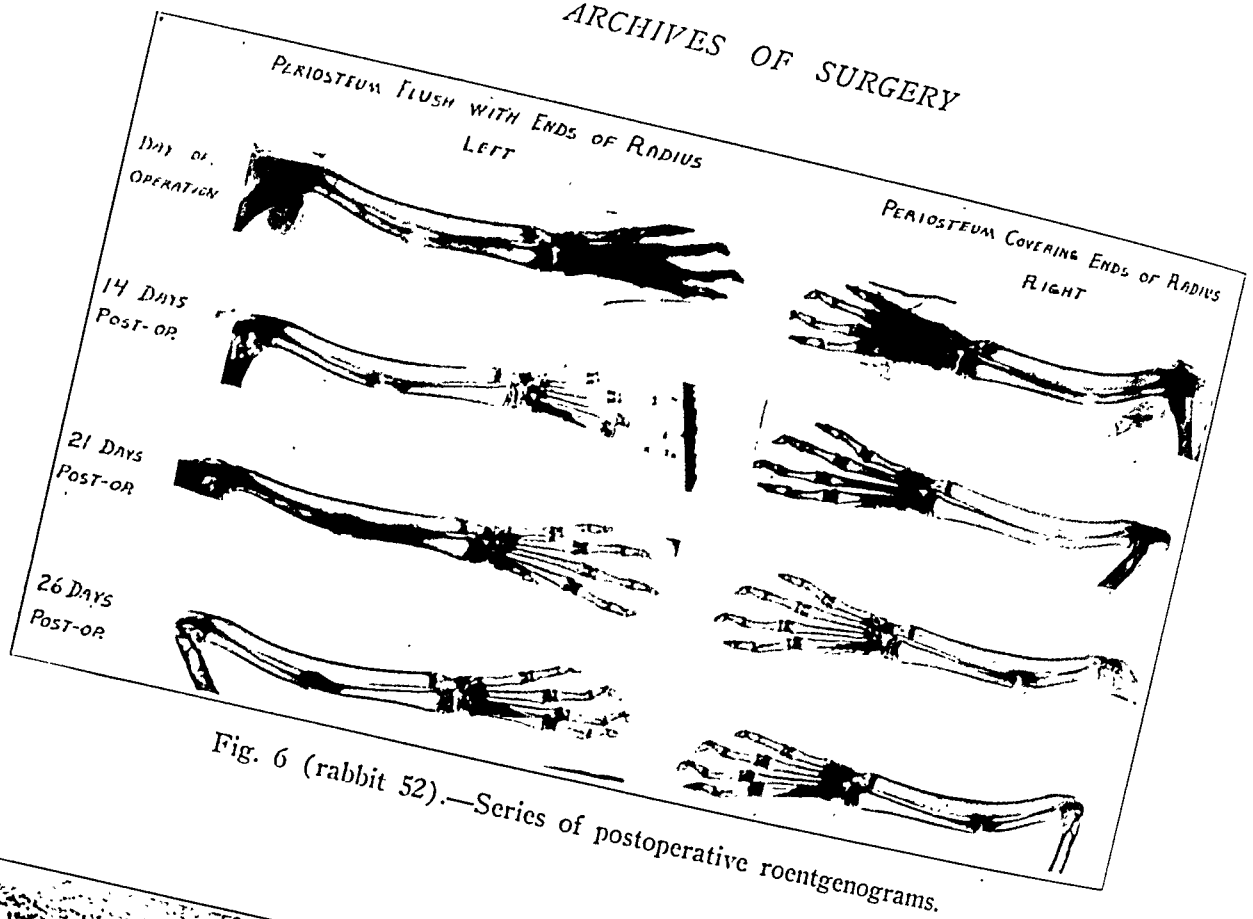


Fig. 5 (rabbit 21).—Photomicrographs of both radii. The section on the left is from the left radius; that on the right, from the right radius.



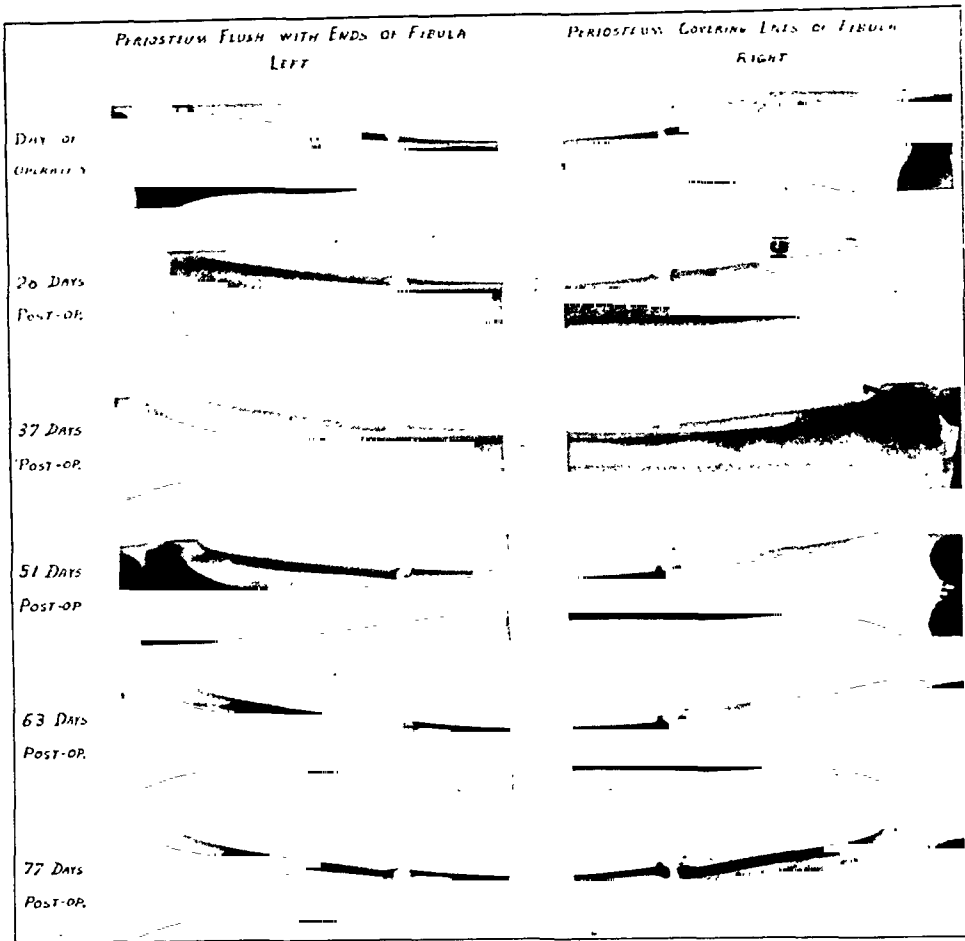


Fig. 8 (dog 41).—Series of postoperative roentgenograms.



Fig. 9 (dog 41).—Photomicrographs of both fibulae. The section on the left is from the left fibula; that on the right, from the right fibula.

from the distal fragment of the left fibula, beginning after four weeks, and not quite bridging the gap at the end of eleven weeks. In microscopic sections of the left fibula (fig. 9), new bone was seen projecting into the defect from both fragments but failing to close the gap. The right fibula presented a bulbous thickening of the end of each fragment, with no effort to close the defect. In microscopic sections, the absence of new bone extending into the gap was apparent. In the other case, dog 43, the defects in both fibulae remained completely open, probably as a result of the interposition of muscle tissue.

These experiments demonstrate the two conditions necessary for the formation of periosteal callus: first, the presence of the cambium layer of the periosteum, and second, the separation of a part of the periosteum from the cortex, thus permitting the accumulation of blood between periosteum and cortex. The value of animal experimentation as compared with clinical observation lies in the normal control possible in the experimental animal but not in the human subject. While different species vary somewhat as to the rate of healing of bone, the general principles obtained from a study of one species can be applied to the others.

CONCLUSIONS

1. Periosteum plays the chief rôle in the healing of fractures.
2. Endosteal (medullary) callus aids in the healing of fractures, but in the absence of periosteum is often unable to complete the union.
3. The interposition of periosteum between the ends of a fractured bone may result in nonunion.

THE ANATOMY OF THE GASSERIAN GANGLION

ITS RELATION TO TIC DOULOUREUX *

F. VAN NOUHUYS, M.D.

LEIDEN, HOLLAND

Before 1900 the surgical treatment for tic douloureux consisted of removal of the gasserian ganglion. Since that time a number of different procedures have been advocated. Spiller (1898) was the first to propose division of the root posterior to the ganglion. Frazier performed this operation in 1901. Korteweg,¹ in 1899, was the first to divide the root. The patient operated on by Korteweg was relieved from pain for twelve years, when it reappeared over the distribution of the first branch. In 1919, Frazier divided only the sensory root, thus preserving the motor division. In 1927, Zaayer² used a more radical procedure. He preserved the motor root, but extirpated the ganglion. Frazier,³ in 1915, performed a partial division of the sensory root.

As a result of phylogenetic and embryologic studies, Frazier came to the conclusion that the peripheral branches of the ganglion were represented in the mesial, central and lateral thirds of the sensory root, a definite topographical relation existing. In discussing the phylogeny, Frazier referred to van Valkenburg's studies. Van Valkenburg⁴ pointed out that in certain animals the fibers of the ophthalmic division are definitely separated from those of the maxillary-mandibular division. Frazier⁵ observed in certain lower forms, reptiles and fishes, that the ophthalmic division has a separate ganglion. The embryologic studies made by Whitehead⁵ showed that in the human embryo the ophthalmic part of the ganglion is separated from the principal part of it by a greater or less distance, and that the fibers

* Submitted for publication, July 30, 1931.

* From the Surgical Clinic of Professor Zaayer.

1. Korteweg: *Algemeene Beschouwingen over de heelkundige behandeling van ziekten van het centrale en het zenuwstelsel*, Geneesk. Bl. mit Klin. en Lab. V. de prakt., Haarlem **17**:261, 1913-1914.

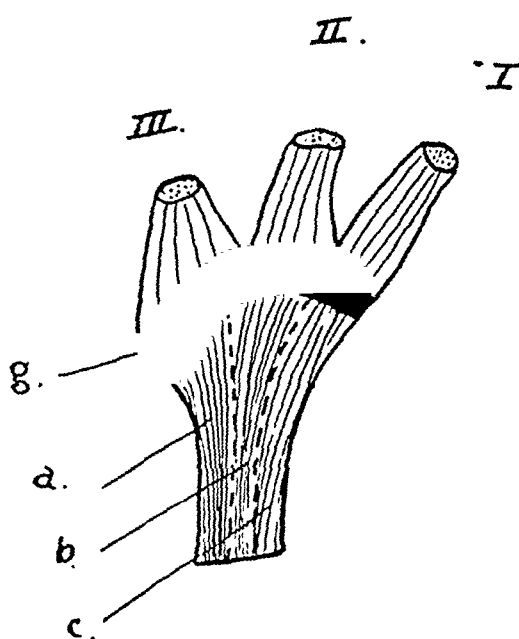
2. Zaayer: *Arch. f. klin. Chir.* **152**:76, 1928.

3. Frazier, C. H.: Subtotal Section of the Sensory Root for Relief of Major Trigeminal Neuralgia, *Arch. Neurol. & Psychiat.* **13**:378 (March) 1925.

4. van Valkenburg: *Folia neuro-biol.*, 1911, vol. 5.

5. Frazier and Whitehead: The Morphology of the Ganglion Gasseri, *Brain* **48**:458, 1925.

of the sensory root run parallel and become arranged in separate bundles by the enveloping supporting tissue and do not tend to intermingle. He gave the following description of the ganglion in an embryo of twenty-eight weeks. The fibers of the sensory root emerge from the hilus of the ganglion as numerous small bundles. These bundles, as they pass upward toward the pons, run more or less parallel, with very little interchange of fibers. He described in older specimens the centripetal fibers as passing centrally in corresponding anatomic thirds of the sensory root. I have not had access to Frazier's⁶ paper, but his opinions are clearly given in the following report: "Anatomisch verlaufen im Ganglion wie in der sensibelen Wurzel die Bahnen der drei Trigeminusäste völlig getrennt von einander und schon



Figs. 1.—Schematic form of the sensory root. In this and the following legends, I stands for ophthalmic nerve; II, maxillary nerve; III, mandibular nerve; *g*, ganglion semilunare; *a*, mandibular part of the sensory root; *b*, maxillary part of the sensory root, and *c*, ophthalmic part of the sensory root.

mit blossen Auge kann man in dem sensibelen Anteil des Ganglionstammes die entsprechenden Stränge zu den Unterabteilungen, resp. den drei Ästen verlaufen sehen. [Anatomically, the channels of the three branches of the trigeminus take the same course in the ganglion and in the sensory root, namely, they are entirely separated from one another, and even with the naked eye one can see in the sensory portion of the ganglion trunk the course of the respective strands to the subdivisions or to the three branches.]” Nothing was found in Frazier’s article concerning the structure of the sensory root in adults.

6. Frazier, quoted in *Zentralbl. f. Chir.* 32:16, 1925.

I have studied the structure of thirty-eight ganglions. These were removed from cadavers.⁷

In none of the ganglions examined were there three anatomically separated parts in the sensory root that corresponded to the three terminal divisions of the fifth nerve. One sensory root, when viewed

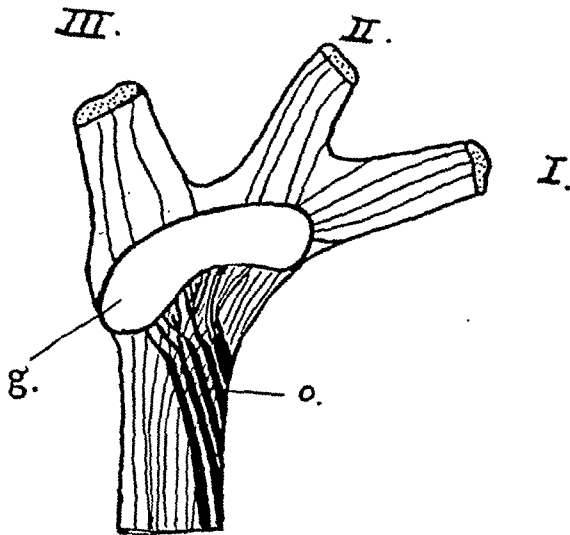


Fig. 2.—Schematic form of the sensory root showing the interlacing bundles of fibers; *g*, ganglion semilunare, and *o*, crossing bundles.

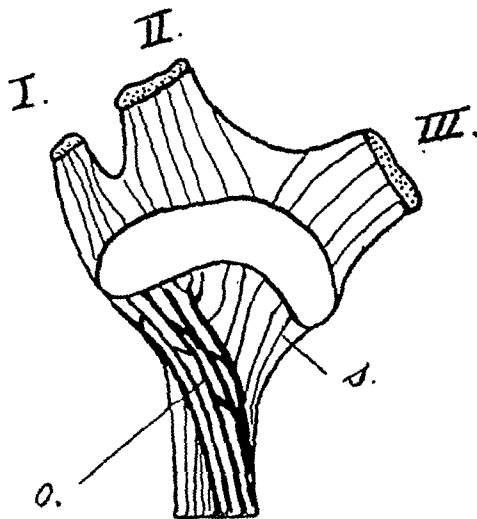


Fig. 3.—Interlacing bundles of fibers are shown here also; *o*, crossing bundles, and *s*, sensory root.

superficially, seemed to have three parts, but more careful examination showed that no division corresponding to the three terminal branches existed.

7. For the technic and more complete details the reader is referred to: Een onderzoek naar de samenstelling van het Ganglion Gasseri in verband met de operatieve behandeling van de Trigemini-neuralgie, Dissertation, Leiden, 1929.

In a sensory root constituted according to Frazier's⁸ idea, a bundle running, for example, in the medial third of the root would not cross at once to the lateral or central portion (figs. 2 and 3). This relation was not found by me to be constant, for in eight instances the fiber bundles crossed from one side of the root to the other.

In hardly any of the sensory roots examined did the bundles run parallel, with very little interchange of fibers. On the contrary, there were, as a rule, many anastomosing and interlacing fibers (fig. 4).

As a rule, the ramifications and anastomoses were most numerous at the hilus of the ganglion, where in some cases there was such a network of fibers that one would be justified in speaking of it as a

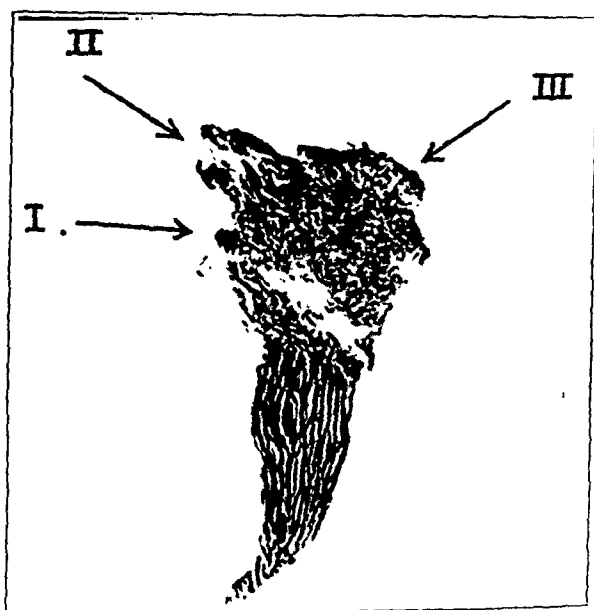


Fig. 4.—Photograph of a sensory root showing anastomosing and interlacing fibers.

plexus. This corresponds to Krause's⁹ description: "Sobald der Stamm des Trigeminus durch den Schlitz den Duralsack verlassen hat, verbreitet sich die sensible Wurzel indem die ursprünglich parallelen Faserbündel auseinanderweichen und sich durch zahlreiche Anastomosen zu einem engwachsigen Geflechte dem Plexus triangularis verstricken welches unmittelbar in das Ganglion gasseri übergeht. [As soon as the trunk of the trigeminus, through the cleft, has left the dural sac, the sensory root becomes broader, in that the originally parallel fiber bundles become separated and interlace by numerous

8. Frazier, C. A.: Operation for Radical Cure of Trigeminal Neuralgia. Analysis of Fifty Cases, *Ann. Surg.* 88:534, 1928.

9. Krause, F.: Die Neuralgie des Trigeminus nebst der Anatomie und Physiologie des Nerven, Leipzig, F. C. W. Vogel, 1896.



Fig. 5.—Photograph showing interlacing of the pathways of the ophthalmic and maxillary divisions of the sensory root. The central bundle in the root received fibers from all the three parts of the ganglion.



Fig. 6.—Photograph of a sensory root showing plexus fibers without any regular arrangement.

anastomoses to a closely woven network, the plexus triangularis, which immediately passes into the gasserian ganglion.]”

Most of the ramifications and anastomoses were found in the medial half of the sensory root. The pathways of the ophthalmic and maxillary divisions interlace a great deal (fig. 5).

In most cases some fiber bundles emerged from the maxillary-mandibular portion of the ganglion to join the motor root (fig. 7).

I have also attempted to learn something about the formation of the ganglion itself. Serial sections of the ganglion were made. There

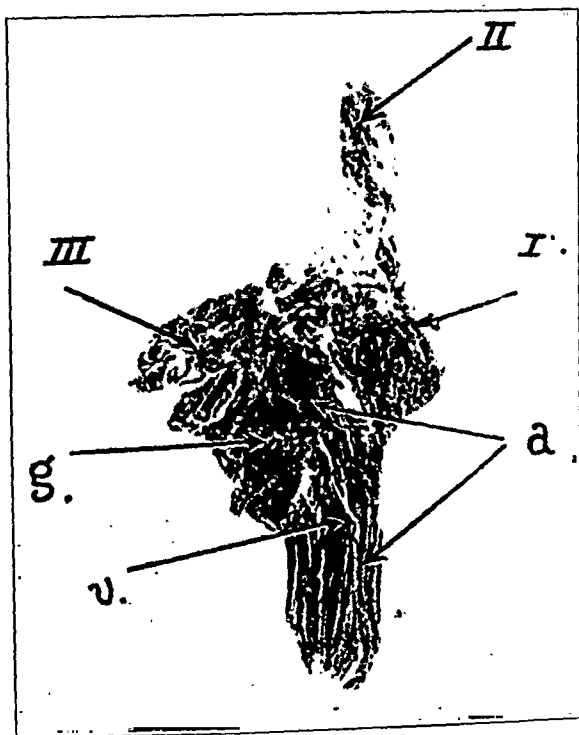


Fig. 7.—Photograph showing fibers bundles emerging from the maxillary-mandibular portion of the ganglion to join the motor root; *g.*, ganglion; *a.*, motor root, and *v.*, two slight fiber bundles joining the motor root.

was no indication that the cell groups represented separate units, or that the interstitial tissue separated definite nerve bundles.

Comparing my findings with those of Frazier, I am unable to agree with his conclusions. Frazier's conclusions are based on the ganglion of the fetus and not on the fully developed ganglion of the adult. It is also certain that in the sensory root of the adult the fibers have no definite parallel arrangement. Certain schematic drawings that have been shown in different articles would indicate that this is the case.

The structure of the sensory nerve varies between two extremes. In one extreme, the bundles may have a parallel course, maintaining the same relation with other bundles throughout the length of the root.

illustrated in figure 1, a schematic form given by Frazier, which I have not found. At the other extreme is an arrangement in which there are no bundles running parallel, but only plexus fibers without any regular arrangement (fig. 6). Between these two extremes many variations may be found. Sensory roots may be found with interlacing bundles of fibers (figs. 2 and 3) and with bundles running practically parallel, but anastomosing frequently and in large numbers.

Dandy,¹⁰ as the result of clinical observations, has come to the same conclusions. In twenty-three cases of tic douloureux in which total section of the sensory root had been made near the pons, he found that only four showed total anesthesia of the skin area supplied by the nerve. In the remaining nineteen more or less sensation was preserved, but there were marked variations in the amount. In three cases all forms of sensations were preserved over the distribution of all branches to about the same degree. The pain of the tic had, however, never reappeared. Dandy, furthermore, stated that after partial section of the root there is not any relation between the part of the sensory root divided and the sensory alterations that follow. The following case was cited by Dandy: The operation of partial section of the sensory root was performed near the pons for pain over the distribution of the supra-orbital nerve. After the operation the sensations of heat and cold were slightly diminished over the distribution of the three branches. The sensations of touch were quite normal. Dandy's conclusions were as follows: "Observations, such as described, deny the hypothesis that the peripheral branches are accurately represented by subdivisions of the sensory root."

Dandy cut the root near the pons, so, with the results cited, the only conclusion that can be arrived at is that the fibers change their position in the distance between the ganglion and the point at which the section is made. Further research will solve the problem.

CONCLUSIONS

1. The sensory root of the fifth nerve is not composed of three parts that correspond to the three peripheral branches from the gasserian ganglion.

2. The operation of partial section of the sensory root, assuming that the pain is carried by bundles having a definite location, is not based on anatomic facts, and therefore cannot be regarded as an absolutely reliable procedure.

10. Dandy, W. E.: An Operation for the Cure of Tic Douloureux; Partial Section of Sensory Roots at Pons, *Arch. Surg.* **18**:687 (Feb.) 1929.

THE BREAKING STRENGTH OF HEALING FRACTURED FIBULAE OF RATS

II. OBSERVATIONS ON A STANDARD DIET *

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It is our purpose in this paper to consider the healing strength of the fractured fibulae of rats on a standard diet. In a preliminary report on this subject, two of us (Dr. Lindsay and Dr. Howes)¹ presented an original method for the determination of the healing strength of fibular calluses in rats from the inception of the fracture to the restitution of normal strength in the healing bone. The findings obtained at that time were in several instances later found to be either inadequate or inconclusive. However, on the basis afforded by this first contribution, the work has been carefully repeated with the result that a much better comprehension of the problem has been made possible. In some instances, important changes were made in technic, while in all cases the factors concerned have been clarified to a greater extent than existed before.

PROCEDURE

We found early that the age and weight range of the rats used in the preliminary work gave too great a disparity in our results; consequently, males from known stock, aged 4 to 8 months, and weighing between 190 and 300 Gm., were eventually chosen for experimentation. As noted in the first paper, the fibula of the rat proved ideal for our purpose for it was firmly splinted by the tibia (fig. 1). As was described previously, the fibula was fractured under aseptic conditions at a point opposite the most prominent point of the crest of the tibia, which we have designated as the "tibial prominence," and the healing strength observed from the sixth to the forty-fifth days postoperatively, at the expiration of which time the fracture was found to be firmly healed. In the case of the animals with fracture, the breaking strength only of the bone was determined. The diet

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* From the Department of Surgery, Yale University School of Medicine.

* The expenses of this investigation were defrayed by Davis and Geck, Inc.

1. Howes, Edward L., and Lindsay, Merrill K.: The Breaking Strength of Healing Fractures, *J. Bone & Joint Surg.* **13**:491 (July) 1931.

was the same as in the preliminary experiment, and in a similar manner relatively complete metabolic data were kept on all animals.

After being on the standard Moise and Smith² diet for one week, the animals were divided into three groups. The first group of fifty rats was free from fracture. At the end of the one week on the diet, they were killed, and the breaking strength of the left and right fibulae was determined. This group was designated the normal normals, and the breaking strength of their fibulae is considered to be the normal breaking strength of unfractured fibulae of rats within similar age, weight

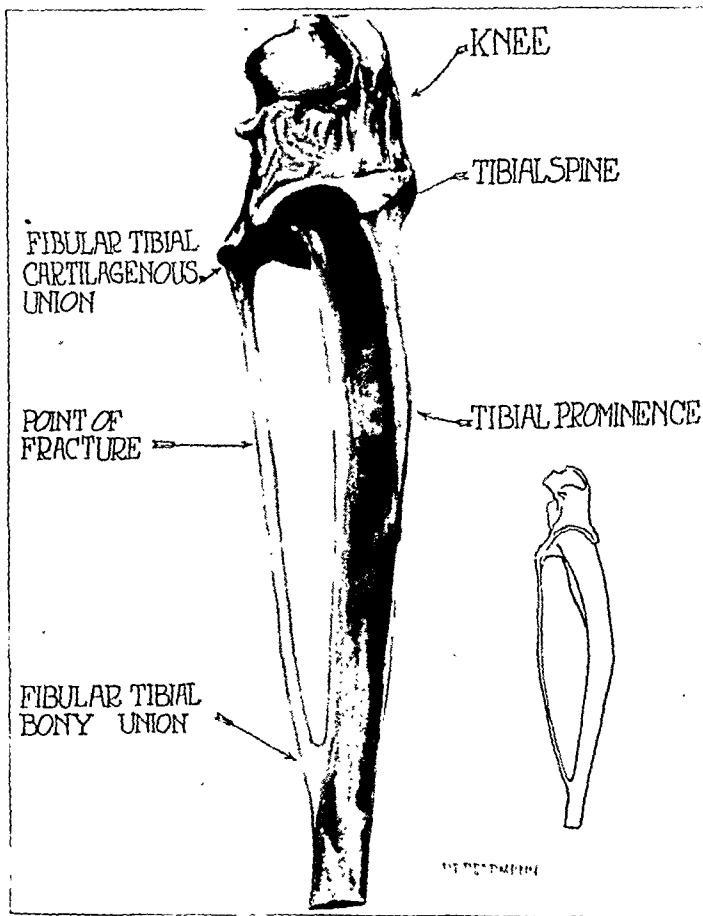


Fig. 1.—Fibula and tibia of the rat. Splinting of the fractured fibula is unnecessary as the tibia holds the fragments in good position.

and dietary limitations. Throughout all the experiments to be undertaken it is hoped that the findings obtained on these animals will serve as a basis on which to compare any other given result.

The second group, known in this paper as the standard controls, resembled the normal normals in that they were free from fracture, but differed in that they were continued on the diet for a greater length of time. These animals were used to determine the effect of the diet on the strength of normal bone. A division of the

2. Moise, T. S., and Smith, A. H.: Diet and Tissue Growth: I. The Regeneration of Liver Tissue on Various Adequate Diets, *J. Exper. Med.* **40**:13, 1924.

standard controls into lots of four was made at the time they were placed on the diet. Beginning on the thirteenth dietary day, and continuing at intervals of three days thereafter to the fifty-second day, one lot was killed for each interval. As will be noted, seven rats with fractured fibulae were killed simultaneously with each four of the standard controls without fracture. Consequently, it was felt advisable to adopt the postoperative intervals for both the animals with and without fracture. These intervals began on the sixth postoperative day and continued every third day thereafter to the forty-fifth day. In other words, there were fourteen postoperative intervals or time periods in which breaking strength determinations were made on four standard controls, as well as on the seven standard animals with fracture to be described.

The third and final group was known as the standard animals with fracture. This group consisted of lots of seven rats, each of which had been on the diet for one week. At the expiration of that time, the right fibula of every animal was fractured in the manner described in the first paper, and a lot of seven animals was

TABLE 1.—*Daily Drying Weights in Grams of Six Pair of Leg Bones of Normal Rats*

	Pair A	Pair B	Pair C	Pair D	Pair E	Pair F
First day (original weight)	1.580	1.365	1.365	1.650	1.590	1.270
Second day.....	0.845	0.865	0.825	0.990	0.935	0.730
Third day.....	0.840	0.845	0.810	0.988	0.922	0.726
Fourth day.....	0.828	0.843	0.817	0.984	0.913	0.715
Fifth day.....	0.822	0.840	0.815	0.980	0.911	0.709
Sixth day.....	0.818	0.838	0.809	0.977	0.909	0.704
Seventh day.....	0.817	0.834	0.802	0.975	0.906	0.701
Eighth day.....	0.814	0.830	0.800	0.974	0.904	0.700
Ninth day.....	0.813	0.828	0.798	0.974	0.903	0.702
Tenth day.....	0.813	0.827	0.798	0.972	0.901	0.702
Eleventh day.....	0.814	0.827	0.797	0.974	0.904	0.702
Twelfth day.....	0.814	0.828	0.799	0.974	0.903	0.703

assigned to each of the fourteen periods from the sixth to the forty-fifth postoperative days. Thus four standard controls controlled seven standard animals with fracture for each of the fourteen periods observed.

On the sixth postoperative day, and at intervals of three days thereafter, the seven standard animals with fracture and the four standard control animals for each period were killed. Measurements of body length, tail length and total length were taken and filed in our laboratory records. Whenever gross pathologic process other than that associated with the fracture was found, the animal was discarded and replaced by another. The fibula and tibia were next prepared as previously described¹ and appeared as in figure 1 when cleaned. It was decided that hereafter a complete histologic examination would be made on all fractures, and this will be reported at a later date. Due to this decision, five pairs of leg bones of the standard rats with fracture were placed in the desiccator over fresh anhydrous calcium chloride, while two pairs were preserved in a diluted solution of formaldehyde, U. S. P. (1:10) for histologic examination. All fifty of the unfractured normal bones were made ready for drying in a manner similar to the foregoing, but none were preserved for histologic study. We became interested in determining the optimum drying time for all these bones as we desired a dry bone and not one wet or "green" which would bend before breaking. We found that drying for seven to ten days removed practically all the moisture from the bones and proved sufficient for our purpose (table 1).

A roentgenogram of one representative fracture from each seven in the particular interval in question was taken, following which the fibular length of every bone was measured and recorded. After drying and measuring the fibulae, the breaking strength was determined on the fibulae of the fifty normal normals, the standard controls and the standard groups with fracture by the technic described in the first paper. In each instance, the strength of both right and left fibulae was noted. The observations were recorded and when indicated were rechecked on additional animals.

The correlations noted in the preliminary report on animal weight, fibular length and breaking strength were gone into in detail. On the basis of these correlations, a formula that we believe to be of considerable value was evolved.³ By its use the disparity in the breaking strength results produced by the variance in weight of the animals selected was considerably reduced. This formula we found of value, not only in interpreting the breaking strength of the normal normals, but of both other groups as well.

Gross photographic studies presenting a picture of the developing callus as seen end on following the breaking of the callus in the beam testing machine were made, and though of some value, did nothing to add to our knowledge. Consequently, they were discarded. Likewise, an attempt to measure the callus of each fracture was discontinued because it did little more than agree with the impression one gained much more comprehensively from the roentgenographic studies. The animal weights and the food intake were again observed, and at this point the notation made in the preliminary paper is worth reiterating; namely, that we have constantly realized that our animals were not in a state of dietary equilibrium after being on the standard diet for but one week. However, our purpose remains to approximate clinical conditions as closely as possible with the material available.

RESULTS

A consideration of the experimental findings is divisible into three phases, i. e., those of the normal normal series, of the standard control lot and of the standard groups with fracture.

I. *The Normal Normal*.—Owing to the range in the weight of the animals of from 190 to 300 Gm., as well as to the differences in age, and other factors, it soon became evident that though we had limited the variables to a greater extent than in the preliminary report, we must develop some common basis on which a more thorough interpretation of the results could be made. This was eventually accomplished through correlations between animal weight, fibular length and breaking strength.

A. *Correlation of Fibular Length to Breaking Strength*: When all animals with fibulae of the same length were placed in groups, and the respective breaking strength of each fibula in each group added, and the arithmetical mean for the group, as well as the combined arithmetical mean for the left and right fibulae in each group determined, it was observed that there was a steady increasing progression in the breaking strength concomitantly with increasing fibular length. This is clearly seen in table 2.

3. William R. Thompson of the department of pathology aided in developing this formula.

On the basis of this it became evident at once that the greater the fibular length, the greater the breaking strength, and from this we plotted the curve seen in figure 2.

B. Correlation of Fibular Length to Animal Weight: Using the same fibular length groups as in the first correlation, we placed under each group the respective weight of the animal concerned. The results are shown in table 3.

From this we note that the longer the fibulae, the heavier the animals. This has been plotted in figure 3.

C. Correlation of Breaking Strength to Animal Weight: It would seem that if length and strength, and length and weight were positively correlated, a similar positive correlation should exist between the

TABLE 2.—Correlation Between Fibular Length and Fibular Strength*

	Fibular Length							
	2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean of breaking strength...	411	358	441	459	460	454	533	495
Combined mean for left and right fibula	384		450		457		509	

* Refer to table 2a for complete data.

TABLE 3.—Correlation Between Fibular Length and Animal Weight*

	Fibular Length			
	2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.
Arithmetic mean of animal weight.....	209	230	251	284

* Refer to table 3a for complete data.

strength and weight. However, this proved by far the most difficult of the three to demonstrate, but was indicated in an arbitrary division of the animals into four groups according to weight, i. e., from 190 to 225 Gm., 226 to 250 Gm., 251 to 275 Gm. and 276 to 300 Gm. In each respective group, the arithmetic mean of the breaking strength for all animals in the group was determined, and a progression found. The results of this are seen in table 4.

The plotted means seen in figure 4 show a steady increase in the breaking strength from the first to the last weight group. Similar correlations were found to exist when a different weight grouping was used, but in the majority of instances they did not show such clearcut results as the one used.

Our results then demonstrated that a correlation existed in each instance between the fibular length, the fibular breaking strength and the animal weight for the fifty animals observed. We have noted earlier that it was our purpose to reduce the breaking strength on all

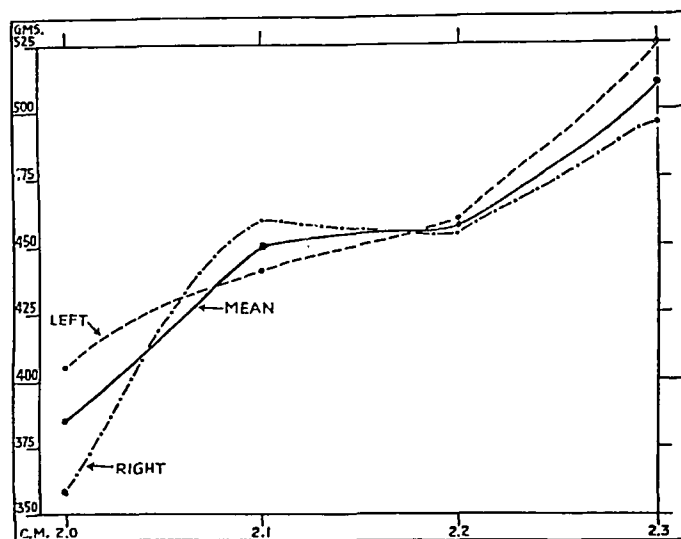


Fig. 2.—Correlation between breaking strength and the length of the right and left fibulae with the combined mean of their breaking strength for normal normal rats. The correlation shows that the longer the fibula is, the greater its strength. The curve of the mean between 2.0 and 2.1 cm. should lie between the curves of the right and left.

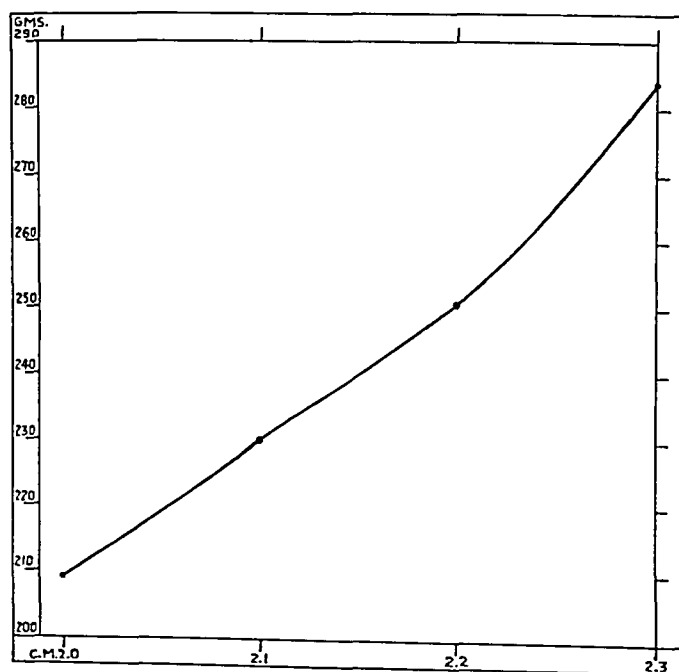


Fig. 3.—Correlation between the weight of the animal and the length of the fibula (where the length of the right equals the length of the left). The results indicate that the heavier the rat, the longer its fibula.

animals used in our experiments to a more common basis, and particularly to adjust the weights in such a manner that the increase in breaking strength concomitant with an increase in weight would present less disparity when the breaking strength was plotted for each of the periodic observations made both in the normal normal group without fracture and in all other rats to be noted subsequently. In other words, our animals ranged from 190 to 300 Gm. in weight, and we had found that the heavier the animal, the stronger the fibula, but we wished to reduce all values by some formula, no matter what the weight, to a point where the great disparity in the breaking strength found on the weight range

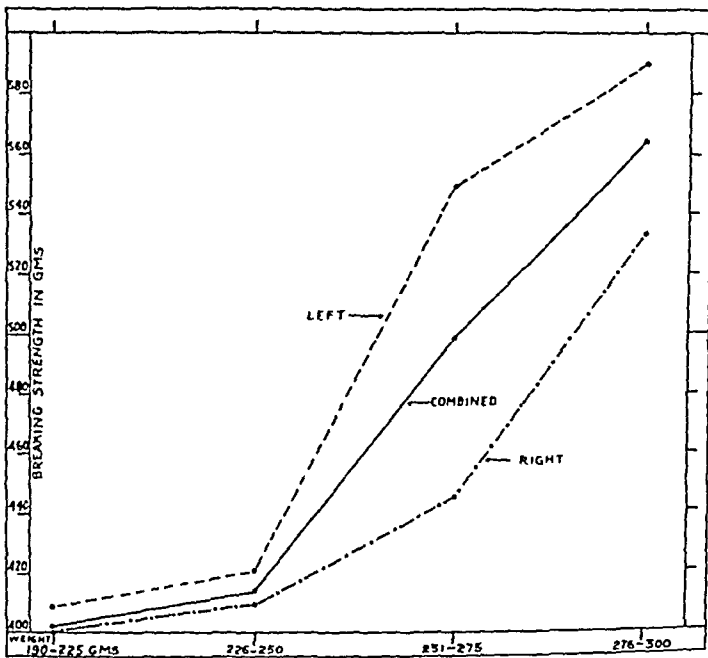


Fig. 4.—Correlation between the weight groups and mean of breaking strength of the right and left fibulae of normal normal rats, as well as correlation between the combined breaking strength means and the weight groups. It is seen that the more the animal weighs, the stronger is its fibulae.

TABLE 4.—Correlation Between Weight and Breaking Strength*

	Weight Groups							
	190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean of breaking strength...	409	394	421	410	550	446	595	533
Combined mean	401		415		498		564	

Refer to table 4a for complete data.

from 190 to 300 Gm. would be reduced, and all animals might be considered as though they were of essentially the same weight.

To develop such a formula, we reasoned as follows: It was observed in fifty determinations that the force required to break the fibulae of the

rat was positively correlated with the animal weight. Undoubtedly this was not the only source of variation, but in order partially to reduce this fluctuation, it was desired to introduce some factor J by which to divide the observed values of F , where F is the force or breaking strength, and J is some function of W , the animal weight, i. e., the normal weight before subjection to fracture and after seven days on diet. As a first approach to a satisfactory solution in this matter, we might consider that all animals used were similar in form (linear

TABLE 5.— $W^{2/3}$ for W from 190 to 300, Inclusive *

W	$(10.W)^{2/3}$	W	$(10.W)^{2/3}$	W	$(10.W)^{2/3}$	W	$(10.W)^{2/3}$
190.....	153.4	220.....	169.1	250.....	184.2	280.....	198.6
1.....	154.0	1.....	169.7	1.....	184.7	1.....	199.1
2.....	154.5	2.....	170.2	2.....	185.2	2.....	199.6
3.....	155.0	3.....	170.7	3.....	185.6	3.....	200.1
4.....	155.6	4.....	171.2	4.....	186.2	4.....	200.6
5.....	156.1	5.....	171.7	5.....	186.7	5.....	201.0
6.....	156.6	6.....	172.2	6.....	187.1	6.....	201.5
7.....	157.2	7.....	172.7	7.....	187.6	7.....	202.0
8.....	157.7	8.....	173.2	8.....	188.1	8.....	202.4
9.....	158.2	9.....	173.7	9.....	188.6	9.....	202.9
200.....	158.8	230.....	174.2	260.....	189.1	290.....	203.4
1.....	159.3	1.....	174.7	1.....	189.6	1.....	203.8
2.....	159.8	2.....	175.2	2.....	190.1	2.....	204.3
3.....	160.3	3.....	175.8	3.....	190.5	3.....	204.8
4.....	160.9	4.....	176.2	4.....	191.0	4.....	205.2
5.....	161.4	5.....	176.8	5.....	191.5	5.....	205.7
6.....	161.9	6.....	177.3	6.....	192.0	6.....	206.2
7.....	162.4	7.....	177.8	7.....	192.5	7.....	206.6
8.....	162.9	8.....	178.3	8.....	192.9	8.....	207.1
9.....	163.5	9.....	178.8	9.....	193.4	9.....	207.7
210.....	164.0	240.....	179.3	270.....	193.9	300.....	208.0
1.....	164.5	1.....	179.8	1.....	194.4		
2.....	165.0	2.....	180.3	2.....	194.9		
3.....	165.6	3.....	180.8	3.....	195.3		
4.....	166.1	4.....	181.2	4.....	195.8		
5.....	166.6	5.....	181.7	5.....	196.3		
6.....	167.1	6.....	182.2	6.....	196.8		
7.....	167.6	7.....	182.7	7.....	197.2		
8.....	168.1	8.....	183.2	8.....	197.7		
9.....	168.6	9.....	183.7	9.....	198.2		

* The result of the division of F by $(10.W)^{2/3}$ was arbitrarily multiplied by 106 in order to reduce the number of decimals, and to facilitate the charting of the results.

dimensions proportional); that breaking strength of the bone was proportional to cross-sectional area at the breaking surface, and that breaking occurs in a similar manner in all instances. If so, then if A is the ratio of a given linear measurement of a given animal to the average or any other arbitrary standard value of this measurement, then the similar ratio (magnitude factor) for the area mentioned would be A^2 and for W the corresponding factor would be A^3 . Now, if we take J proportional to A^2 we have a solution. Accordingly,* we took

* The choice of the value $J = (10.W)^{2/3}$ may seem strange, but it was employed to coincide with results of preliminary calculations where $J = W^{2/3}$ was taken with W in decigrams.

$J = (10.W)^{2/3}$ or the real cube root of the square of $(10.W)$. The formula would then be $\frac{F}{(10.W)^{2/3}} = R$ (ratio). To facilitate the determination of $(10.W)^{2/3}$, we have prepared table 5 for W from 190 to 300 Gm. inclusive (table 5).

With the aid of this formula, we corrected all our breaking strength determinations on the normal normal rats as may be seen in table 6.

TABLE 6.— $\frac{F}{W^{2/3}} = R$ (Fifty Normal Normal Rats)*

	W	Weight (10.w) ^{2/3}	F Left	F Right	R of Left	R of Right
Arithmetic mean	243	177	458	440	252	243
Standard deviation mean.....	20	19	9	9

* Refer to table 6a for complete data.

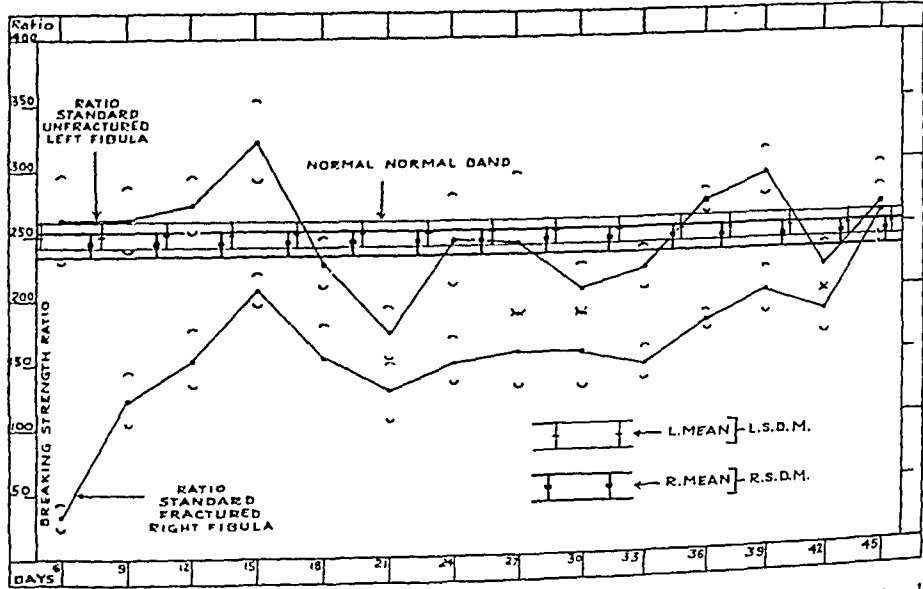


Fig. 5.—The breaking strength ratios of the normal normals and the standard groups with fractures. The straight band represents the normal normals. The mean of the left fibula is 9 greater than that of the right (L. Mean and R. Mean). The standard deviations of the mean depreciate this difference somewhat (L. S. D. M. and R. S. D. M.). The band indicates the ratios of fifty normal rats and affords a basis with which to compare ratios obtained on the different diets used. The primary callus has formed in the fractured right fibula by the fifteenth day. The medullary cavity develops by the twenty-first day. Thereafter strength is restored by cortical thickening and callus reorganization. Healing is theoretically complete by the forty-fifth day. The unfractured left fibula rises and falls simultaneously with the right. This may indicate a generalized skeletal response to the fracture.

When the ratios were plotted, we found a broad band passing across the chart with the left fibula stronger by a ratio of 9 than the right. However, if the standard deviations for the left and right are determined, it is observed that there is considerable overlapping of the two and that the difference is not significant (fig. 5).

The normal normal band, composing as it does the breaking strength ratio of the fifty normal animals, is considered throughout our work as representing the values on normal animals within the weight group used. In the case of healing fractured right fibulae, both of animals in the standard series with fracture and possibly of those on all diets, healing may be considered to be complete when the strength of the fracture falls within or above this band, but our work is not yet sufficiently advanced with other diets for us to be certain of this. In a similar manner, plotted variations in the strength of the unfractured left fibulae in the standard groups with fracture can be seen clearly by use of the band, and our reason for assuming that the unfractured left fibulae in the animals with fracture cannot be used to control the fractured right fibulae will become apparent when we note later the marked fluctuations to one side or the other of the band that the unfractured left fibular ratio of the standard group with fracture presents.

II. *Standard Control Group.*—The results obtained on this group of animals are of particular interest for two reasons. For one thing, the breaking strength ratio of the standard controls compared both with the ratios of the normal normals and of the standard group with fracture proved quite interesting. For another thing, the difference in the metabolic reaction of the standard control rats to that of the standard group with fracture was very clearcut. Correlations between animal weight, fibular length and fibular strength on the standard control animals were also made in a similar fashion to those drawn on the normal normals.

A. *Breaking Strength:* The ratios for the left and right fibula, respectively, lie, as we found in the normal normals, in close proximity. When they are considered together it is noted that they fall from around 330 on the sixth day period to a low point on the eighteenth day of approximately 175. This is followed by an abrupt rise to about 285 on the twenty-fourth day which is the highest ratio reached throughout. A fall to 150 occurs by the thirty-third day, and a rise with a slight fall thereafter follows on the forty-second and forty-fifth days, respectively. In table 7 the respective ratios with their standard deviations are recorded, while in figure 6 the ratios have been plotted.

When we compare the ratios of the breaking strength ratios of the right and left fibulae of the standard control group in figure 6 with those of the normal normals, as is plotted in figure 5, we observe that the control ratios fluctuate widely on either side of the normal normal means. Consequently, we believe that it is a justifiable assumption to state that the strength of the standard controls throughout showed a progressive loss in strength directly proportional, within limitations, to the length of time on diet. At a later point a comparison between the control and the fracture ratios will be made.

B. Correlations: In a similar manner to that observed on the normal normals, correlations between animal weight, fibular strength and fibular length were made for the standard controls. It was found that such correlations could readily be made, and that though the means differed, the progress of the curve was essentially the same.

TABLE 7.—*Breaking Strength Ratio of Right and Left Fibulae of Standard Control Group **

Postoperative Days	Standard Deviation Mean R for Left With	Standard Deviation Mean R for Right With
6.....	333 ± 11	319 ± 5
9.....	255 ± 20	241 ± 16
12.....	231 ± 39	244 ± 50
15.....	186 ± 4	186 ± 8
18.....	175 ± 6	169 ± 8
21.....	216 ± 20	182 ± 16
24.....	285 ± 23	282 ± 25
27.....	270 ± 43	252 ± 25
30.....	207 ± 10	201 ± 14
33.....	151 ± 18	152 ± 14
36.....	188 ± 18	169 ± 19
39.....	213 ± 13	199 ± 9
42.....	222 ± 16	226 ± 20
45.....	218 ± 12	209 ± 15

* Refer to table 7a for complete data.

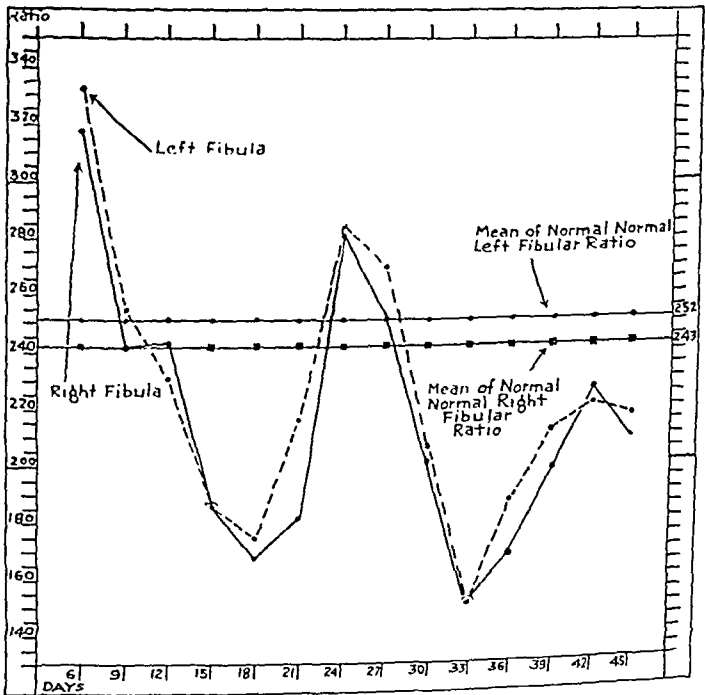


Fig. 6.—The breaking strength ratios of the standard controls without fractures compared with that of the normal normals. The relatively close agreement between the ratios of the standard right and left fibulae is seen. The somewhat irregular, but progressive loss of strength proportional to the time the animals are on diet is clearly brought out. This furnished the first lead that the normal bone strength is strongly influenced by the diet and body weight.

The weight and length were correlated as they had been in the normal normals with the results seen in table 9.

Under the normal normals, we arbitrarily divided the animals into groups according to weight. A similar division was made here, but it was found that a less striking correlation existed. This might be attributed to the small number and otherwise unsatisfactory character of animals selected in the division from 251 to 275 Gm. When this was corrected, as it was when the high fat and high carbohydrate diets

TABLE 8.—*Correlation Between Fibular Length and Strength **

	2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean of strength.....	303	298	317	299	400	388	526	576
Combined mean	303		303		394		520	

* Refer to table 8a for complete data.

TABLE 9.—*Correlation Between Fibular Length and Animal Weight **

	2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.
Arithmetic mean of weight.....	214	223	233	278

* Refer to table 9a for complete data.

TABLE 10.—*Correlation Between Animal Weight and Fibular Strength. **

	190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean of strength.....	303	289	373	373	593	566	528	504
Combined mean	296		373		580		516	

* Refer to table 10a for complete data.

were used (to be reported later), it was found that a stronger correlation between animal weights and fibular strengths could be drawn for the control rats as well as for the normal normals.

C. Data on Food Intake and Weight of Rats: The results of the metabolic studies are not sufficiently detailed to afford conclusive observations, but their relative value has proved quite worth while for our understanding of the problem of the healing of fracture on the various diets undertaken.

In the case of the standard control animals our data have been compiled with two ends in view. The first was to determine what percentage difference in weight took place in the rats from the sixth day on the diet until they were killed which was determined by estimating the gains and losses in weight on the day of killing as percentage of body weight on the sixth day. The second end sought was to deter-

mine the food consumed per day in terms of percentage of body weight from the time of operation until the rats were killed.

When these two values were determined, it was noted that from the sixth day on there was a steady though somewhat irregular loss in the weight of the rats, as well as a slight but progressive diminution in their food intake. These observations have been recorded in table 11.

When the percentages are plotted, we note that the picture of steady loss of weight and decreased food consumption is brought more clearly to our attention. In figures 7 and 8 we have charted the percentage along with those for the standard group with fractures with which they will later be compared.

TABLE 11.—Data on Food and Weight *

Days	Difference in Weight From Operation to Time of Killing as per Cent of Weight on Sixth Day	Food Consumed per Day From Operation to Time of Killing as per Cent of Weight on Sixth Day
6.....	— 2.25	3.75
9.....	— 4.25	3.33
12.....	— 4.64	3.37
15.....	— 3.77	3.30
18.....	— 7.11	3.46
21.....	— 7.20	3.44
24.....	—15.02	3.43
27.....	—12.03	3.11
30.....	— 6.35	2.92
33.....	—12.76	2.93
36.....	—11.45	3.39
39.....	—11.06	2.92
42.....	—16.27	2.99
45.....	—18.39	2.82

* Refer to table 11a for complete data.

III. *Standard Fractured Group.*—These animals probably constitute the most important series of this problem. The results obtained are divided for purposes of greater clarity into several subheadings.

A. *Gross Examination of the Fracture:* The gross appearance of healing fractures has been repeatedly studied by other workers. However, we have observed selected fractures under the dissecting microscope from the sixth to the forty-fifth day in this group of rats. An irregular translucent and somewhat gelatinous appearing tissue was at first seen about the site of the fracture. This possessed a spindle shape and was of greater diameter about its mesial portion and fused into the shaft peripherally. By the fifteenth day the previously soft structure had become firm, granular and opaque. From the fifteenth day on there was a gradual transformation of the callus into a smooth, regular and firm structure.

When the callus was examined end on after being subjected to and broken in the beam test, a much better picture of the healing process was

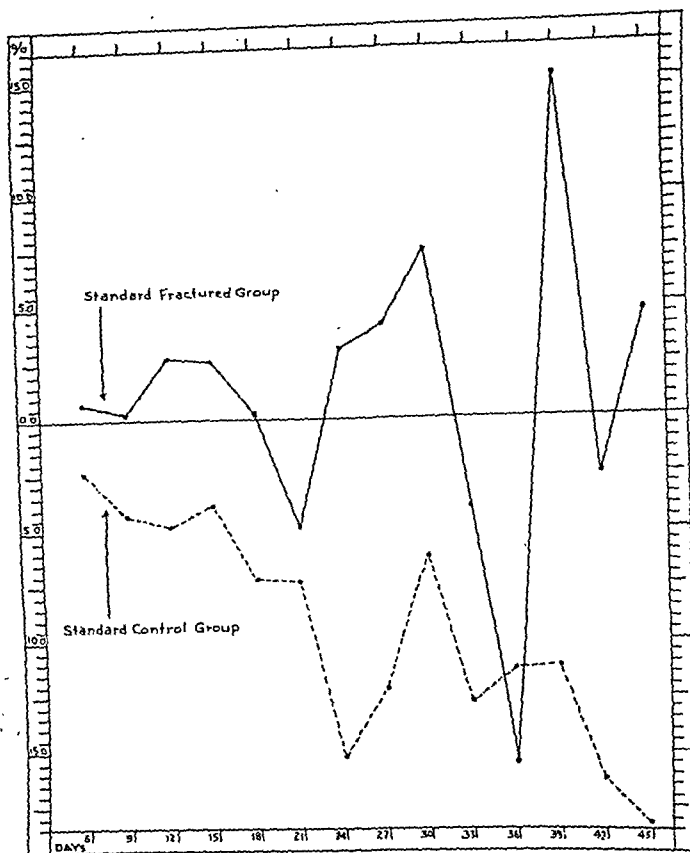


Fig. 7.—Curve showing the difference in weight from operation until the animal was killed (plotted as per cent of body weight at operation). The early stimulating effect of the injury is observed in the rats with fractures. After the formation of the primary callus on the fifteenth day, the weights of the lot with fractures fluctuated widely, but with a constant tendency to increase. The controls lost weight from start to finish. Simultaneously with falling weight, we have already seen in figure 6 that the fibular strength diminished.

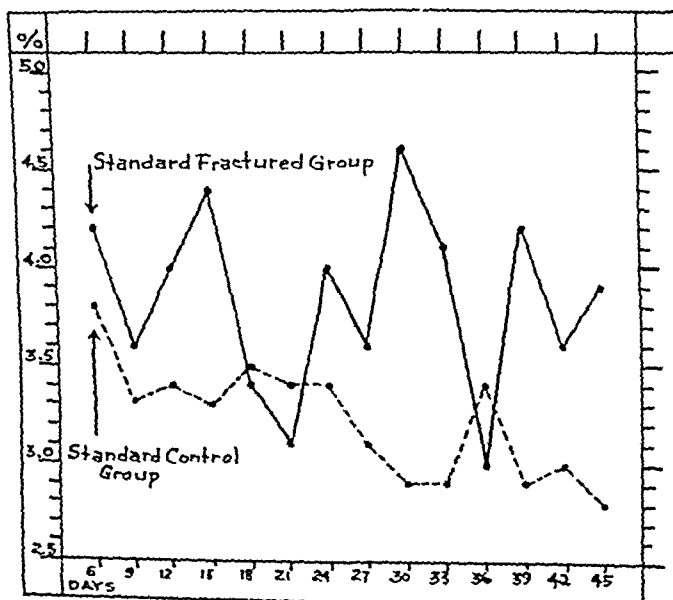


Fig. 8.—The food consumed per day (represented by curve plotted as per cent of body weight at operation) from operation until the animal was killed, for both the animals with fracture and the control series, varied considerably. This was particularly true of the rats with fracture. However, as food intake fluctuated, both body weight and fibular strength simultaneously increased or decreased.

observed. By the fifteenth day it was seen to have become entirely impregnated with salts throughout its cross-sectional area. Thereafter there grew into this solid mass of salts countless fine blood vessels which by the thirty-third day had almost entirely fused medially to form the medullary cavity. The cortex simultaneously thickened slowly, and the diameter of the callus diminished, until by the forty-fifth day the process appeared complete.

B. Diameter of the Callus: Representative calluses were measured for each observed period. The measurements, though incomplete, substantiated the opinion given by the gross examination that the diameter

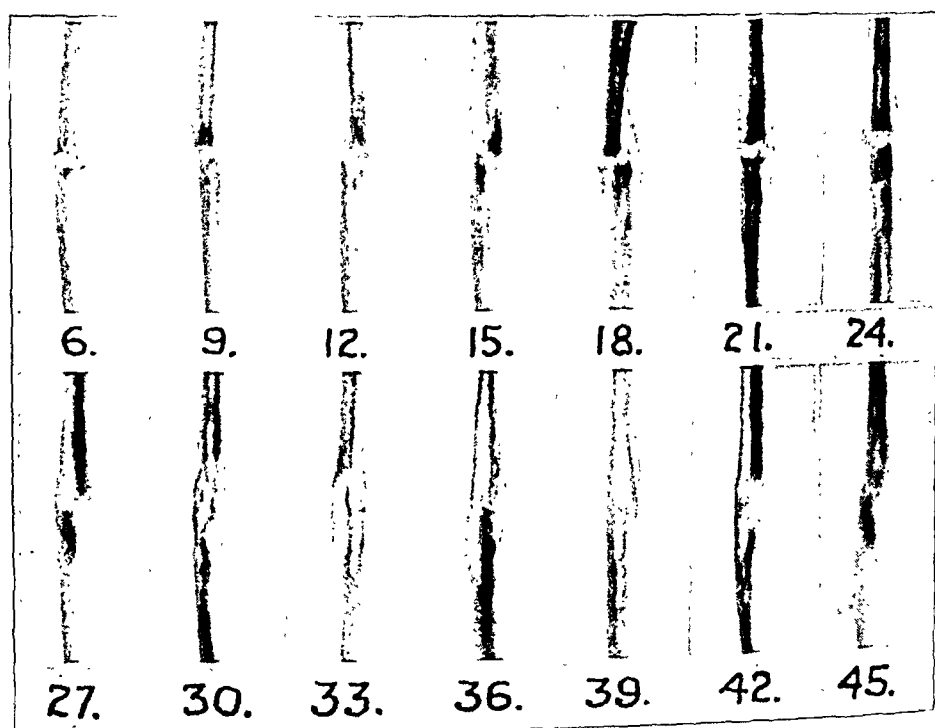


Fig. 9.—Roentgenograms of typical fractures at intervals of three days from the sixth to the forty-fifth postoperative days. The primary callus was formed by the fifteenth day. The medullary cavity is well developed on the twenty-first day. Thereafter the cortex thickened and the callus reorganized. The strength of the callus after the fifteenth day was found to bear only slight relation to the degree of density observed in the roentgen studies. Magnification, $\times 3.5$.

increased to the fifteenth day and diminished thereafter. The diameter throughout did not, however, at any time become reduced to that of the diaphysis.

C. Roentgenographic Examination: It was observed from the roentgenographic studies for each period that the apposition of the fracture was good and angulation reduced to a minimum. From this we believe our policy of not splinting the fracture is vindicated.

From the sixth to the fifteenth day, inclusive, a progressive enlargement in the diameter of the callus was seen in the x-ray films. A similar increase in density took place with a noticeable irregularity in the salt depositions. The fractured fibular ends were seen to be undergoing decalcification simultaneously with increasing density of the callus (fig. 9).

Between the fifteenth and thirty-third days, irregularities in opacity are noted in the roentgenograms as the processes of modeling, cavitation, and formation of the medullary cavity occur. Following this, and in fact occurring simultaneously, cortical thickening and reshaping of the

TABLE 12.—*Breaking Strength Ratio of Fractured Right and Unfractured Left Fibulae **

Day	Ratio	
	Fractured Right	Unfractured Left
6.....	33 \pm 8	264 \pm 32
9.....	124 \pm 21	262 \pm 24
12.....	153 \pm 22	274 \pm 20
15.....	208 \pm 13	326 \pm 29
18.....	156 \pm 26	228 \pm 19
21.....	128 \pm 19	172 \pm 21
24.....	149 \pm 18	245 \pm 32
27.....	168 \pm 31	243 \pm 50
30.....	167 \pm 29	207 \pm 16
33.....	157 \pm 14	220 \pm 17
36.....	179 \pm 9	274 \pm 13
39.....	202 \pm 19	294 \pm 20
42.....	184 \pm 17	217 \pm 18
45.....	258 \pm 23	269 \pm 31

* Refer to table 12a for complete data.

previously roughened, irregular callus takes place, until on the forty-fifth day a healed fibula of comparatively uniform density has developed.

D. The Breaking Strength: The breaking strength was observed on both the fractured right and the unfractured left fibulae, and, as the results obtained differ decidedly in each, they are considered separately.

1. Fractured right fibula:

All breaking strength results were expressed in terms of the ratio or R, and are so described.

There was a sharp rise in R from the sixth to the fifteenth day coincidentally with increasing salt precipitation as indicated both on gross and roentgenographic examination. R on the fifteenth day was 208 ± 13 which, as may be seen on table 12, was the highest point reached in the stage of primary callus formation (table 12).

Subsequent to the fifteenth day, an abrupt fall during the eighteenth and twenty-first day occurred, reaching a low point of 128 ± 19 . This took place simultaneously with the development of the medullary cavity.

as was noted in the gross examination. Apparently there can be little doubt that the inbudding blood vessels, forming the medullary space by their fusion, weaken the callus.

From the twenty-fourth day, the breaking strength steadily rose with slight variations from time to time. This we would expect both from the roentgenograms and the gross examination, for we have previously found that as the medullary cavity developed, the cortex thickened and the callus reorganized.

By the forty-second day the ratio reached 184 ± 17 , and was followed by a rapid incline to 258 ± 23 by the forty-fifth day. The rise was striking and well defined. The ratio on the forty-fifth day fell within the normal normal band passing across figure 5, and consequently was considered to be the end-point. In addition, the arithmetic means of the ratio fell within the standard deviation of the mean for the unfractured left fibula.

2. Unfractured left fibula: It becomes apparent at once when figure 5 is examined why the unfractured left fibula cannot be used as a control for the fractured right fibula. The plotted ratios for the left fibulae do not present a moderately straight line similar to that of the normal normal band, nor do they possess any of the characteristics of the unfractured left fibulae in the standard controls, as seen in figure 6. On the contrary, the left fluctuates in strength, as does the right, and surprising as it may seem, these fluctuations roughly occur simultaneously with similar increases and decreases in the healing strength ratios of the fractured right fibulae. Consequently, attempts to plot the ratios of the right in terms of percentage of the left fibulae are impossible.

The exact ratios of the left fibulae as given in table 12, and as plotted in figure 5 show these fluctuations clearly and afford a ready table of results from which to conclude that we cannot call the left normal, nor can we use it to control the right. The explanation of this is at present problematic, but possible theories will be discussed later.

E. Data on Animal Weights and Food Intakes: The metabolism of the standard groups with fracture was studied in a manner similar to that of the standard controls, and the same compilation of data was made. The data have been plotted along with that of the controls in figures 7 and 8.

The animals with fracture showed a moderate but readily identifiable gain in weight from the sixth to the fifteenth day, at which time, simultaneously with a sharp loss in the strength of the callus, the increasing weight reversed its course and fell from plus 2.6 per cent on the fifteenth day to plus 0.4 per cent on the eighteenth. By the twenty-first day the percentage had dropped to minus 4.7 per cent. The

percentage then rose to plus 7.5 per cent on the thirtieth day only to be followed by a sharp and rapid fall to minus 15.5 per cent by the thirty-sixth day. Thereafter it rose to plus 15.1 per cent on the thirty-ninth day, fell to minus 2.7 per cent on the forty-second day and rose and ended with plus 4.7 per cent on the forty-fifth day as is seen in table 13.

The interesting point of the differences in weight from operation until the animal is killed as percentage of body weight at operation lies in its correlation with the breaking strength ratios. An agreement apparently exists as shown by a rising percentage up to the fifteenth day, simultaneously with the greatest strength in the primary callus, but thereafter the correlation is hard to draw. The elevation of

TABLE 13.—*Body Weight and Food Intake* *

Day	Difference in Weight From Operation to Time of Killing as per Cent of Weight at Operation	Food Consumed per Day as per Cent of Body Weight at Operation
6.....	+0.9	4.2
9.....	+0.1	3.6
12.....	+2.0	4.0
15.....	+2.6	4.4
18.....	+0.4	3.4
21.....	-4.7	3.1
24.....	+3.2	4.0
27.....	+4.4	3.6
30.....	+7.5	4.6
33.....	-4.0	4.1
36.....	-15.5	3.0
39.....	+15.1	4.2
42.....	-2.7	3.6
45.....	+4.7	3.9

* Refer to table 13a for complete data.

metabolic percentages on the thirtieth day occurs coincidentally with the completion of the stage of modeling and the formation of the medullary cavity. However, the subsequent fall may be due to individual variations in the animals on the thirty-sixth day or to some other metabolic factors at present unknown. Likewise, the sharp rise on the thirty-ninth day to an opposite extreme from the loss on the thirty-sixth day is inexplicable. These will be discussed at a later point in this paper.

The food consumed per day observed as percentage of body weight at operation, and plotted in figure 8, agrees in a similar fashion to that found for the standard controls with the weight percentages in that with loss of weight the food consumed diminished, and concomitantly with gain in weight there was an increase in food consumption.

It is especially notable that on the fifteenth day the percentage of food consumed was 4.4 per cent at which time the primary callus was at

its greatest strength. With the loss in strength in the callus, the food consumption diminished. On the thirtieth day the percentage was at + 4.6 per cent, which was its greatest height. Table 13 gives the data for both the weight and food percentages.

COMMENT

The value of the beam testing machine for determining the healing strength of fractured fibulae of rats, as well as the normal breaking strength, appears unlimited, but actually it possesses definite limitations which will be discussed later. However, the simplicity of its mechanism and the comparative accuracy of its determinations warrant a careful consideration of the results obtained from it.

On the normal normal rats the correlations observed between fibular length, fibular strength and animal weight substantiated the findings of several previous workers, but the correlation shown to exist between the animal weight and the breaking and healing strength of the fibula proved to have an added value. Through this correlation we developed the formula $\frac{F}{(10.W)^{2/3}} = R$, by means of which we were able to discount considerably the variations in breaking strength due to the disparity in the animals' weight from 190 to 300 Gm. The band resulting from the observations on the normal normals gave us a comparative guide by means of which we could adjudge the degree of normalcy of any given determinations within similar weight and age limits.

The standard control group, being free from fractures and on the standard diet for the same interval in each period as a similar group of the standard animals with fracture, proved to be of considerable merit from two angles. In the one case it was found that the trend of the breaking strength of this group fell or diminished in direct proportion to the duration of time they were on diet. True, there was a rise of the breaking strength on the twenty-fourth day, but throughout the trend was downward. In the second instance, this group showed a steady loss of body weight and a diminution in the quantity of food consumed. Again, there were found fluctuations in the two curves presenting these results, but their course was a constantly decreasing percentage from beginning to end. The apparent correlation between loss in fibular strength and loss in animal weight may be attributable to the influence of the diet on the metabolism of the bone, especially on those metabolic factors that determine the strength of the bone.

The unfractured left fibula in the standard fractured series fluctuated in strength concomitantly with similar fluctuations in the healing strength of the fractured right fibula. As the primary callus increased in strength to attain its highest level on the fifteenth day, the strength

of the left likewise rose, and as the callus lost strength (seemingly through formation of the medullary cavity) the left also showed diminished breaking strength. Moreover, with subsequent cortical thickening and increased strength in the fracture, the strength of the unfractured left fibula also increased. At first glance one is strongly inclined to believe that this reaction presents evidence that the fracture is producing not a local response to injury, but rather a generalized skeletal reaction by means of which the skeleton fluctuates in strength as the fracture fluctuates. There seems little reason to doubt this within limitations. It is true that the unfractured left fibula may be varying in strength due to neurogenic stimuli arising in and crossing over from the fractured right fibula with consequential variations in blood supply to it, but we have found that the radii of the forelegs vary in strength also, so this cannot be the entire picture. It is also quite possible that phosphatase and the parathyroid hormone as personally suggested by Kay are factors in the rise and fall of strength in the left fibula, and this deserves special consideration.

Phosphatase is an enzyme found especially in growing bone which possesses the power to transform the organic phosphate compound to an inorganic one in which form it is found in the bone. Kay⁴ determined that phosphatase exists in the circulation as well as in the growing epiphysis; in fact, in various bone diseases he recently found in some cases remarkable changes in the blood phosphatase level. In our laboratories, Ostergren and one of us (Dr. McKeown) showed in an unpublished preliminary study that the phosphatase of the rat skeleton with a fractured right fibula rises to the fifteenth day, and thereafter falls slowly back to its starting point. We saw in our gross examination of the callus, mentioned earlier in the paper, that the healing fracture became heavily impregnated with salts by the fifteenth day. In explanation of this, Harris⁵ called our attention to the fact that this occurs in cartilage cells past the height of their growth curve and in the presence of an extremely small quantity of tissue fluid. He apparently would have us believe that calcification occurs in a diminished circulation of tissue juices and associated with vitamin D. Fell and Robison,⁶ in cultivation in vitro of embryonic limb buds, found phosphatase formed by hypertrophic cartilage cells only. Thus, we seem to be confronted with two phases of phosphatase activity. A local response occurring

4. Kay, H. D.: Plasma Phosphatase: II. The Enzyme in Disease Particularly in Bone Disease, *J. Biol. Chem.* **89**:249, 1930.

5. Harris, H. A.: Cod Liver Oil and the Vitamins in Relation to Bone Growth and Rickets, *Am. J. M. Sc.* **181**:453 (April) 1931.

6. Fell, H. B. and Robison, Robert: The Growth, Development and Phosphatase Activity of Embryonic Avian Femora and Limb Buds Cultivated in Vitro, *Biochem. J.* **23**:767, 1929.

at the fracture site simultaneously with cartilage formation and leading to calcification of the callus with increasing strength therein until the fifteenth day, and a generalized skeletal reaction occurring coincidentally, which we may assume to be due either to an overflow of phosphatase from the fracture or a stimulation to increased phosphatase production occurring at all phosphatase centers in response to a substance elaborated by the fracture, and in either case resulting in greater skeletal strength from accelerated calcification. This is to no small extent hypothetical at the present time, but yet may afford a basis for future advances along this line.

The falling strength noted in both the standard fractured right and left fibula may possibly be due to parathyroid hormone. It is difficult to believe that the mere mechanical activity of osteoclasts, or the fusing of the medullary blood vessels to form the medullary cavity, could in the space of six days produce the abrupt fall in strength seen in the healing fracture. Likewise in the fractured left fibula, since we are not confronted with a developing medullary cavity, we cannot at present assume any accelerated osteoclastic activity. As in the case of increasing strength and phosphatase, we are then confronted with the fact that the falling strength must be due largely to a circulating substance, and such a decalcifying substance that would produce falling strength could conceivably be the hormone of the parathyroid glands. We may then assume that phosphatase and parathyroid hormone are antagonists in the sense that the first accelerates calcification while the second accelerates decalcification.

However, although all the foregoing assumptions are attractive, there still remain several results to consider that are not only interesting but afford a basis for very appealing speculations. It will be recalled that on the normal normals we found the more the animal weighed, the stronger was its fibula. There seems no reason why this should not be stated in the reverse order; namely, that the lighter the animal, the weaker the bone. Turning to the breaking strength of the standard controls, we see that there was a progressive loss in strength from the sixth to the forty-fifth days, and that with this diminution the weight of the rats and the food they consumed fell from the beginning to the end of the experiment. Consequently, with this decrease in food and weight, the animals became lighter, and, becoming lighter, the strength of their fibulae fell. This was an important observation, for it may go far to explain the fluctuations observed in the breaking strength of the unfractured left fibula in the standard series with fracture.

The strength of the unfractured left fibula rose on the fifteenth day, while the weight as well as the food intake had also risen by the same day. Between the fifteenth and the twenty-first days, the strength fell

and, at the same time, the body weight and the quantity of food consumed decreased also. This agreement between strength of the fibula, animal weight and the amount of food consumed exists throughout. There are sharp rises and falls, but, in general, this comparatively close relationship of one to the other is readily seen.

We know that the increasing strength in the fractured right fibula up to and including the fifteenth day is due to the formation of the primary callus. The simultaneous gain in weight throughout this interval we assume to be due to the stimulated metabolism occurring in the early reparative state that is said by workers in the field to follow any extensive tissue injury. Harvey and Howes obtained strong evidence to support this opinion in their studies on wound healing in the rat.

After the fifteenth day the healing strength of the fractured right fibula falls to the twenty-first day, only to rise again through a slow sweeping curve. The nature and the relative smoothness of the curve could be better seen if the line were to be drawn without attempting to include the arithmetical means of each periodic observation. Such a curve would then be not irregular with peaks and valleys, but rather even and regular. It would probably take the form of a sigma, and be expressive thereby of a chemical reaction. One is led to wonder if the body weights and the food intake were constant from beginning to end of the experiment, if such a curve would not be obtained.

Although we may surmise that the animal weight and the fibular strength are closely correlated, we still find ourselves at sea in respect to the mechanism that adjusts the weight to produce the variations noted in the strengths from interval to interval. There is an undoubted factor of uniformity in the influencing agent, as we can see when the fibular strengths are studied. Harris,⁵ as we noted before, would have us believe that vitamin D controls calcification while vitamin A regulates the process of ossification. There seems no occasion for us to believe that the quantity of these vitamins available for absorption varies, but possibly the fracture elaborates a substance essential to the activity of the vitamins and which also influences the animals' desire for food.

To consider the roentgenograms obtained in these studies, it has been pointed out by Eliason⁷ that the usefulness of the roentgenogram as an index of the degree of healing in the fracture is only during the period of primary callus formation. This was further emphasized in our studies. The roentgenogram outlined a maximum callus on the fifteenth day which agreed with the breaking strength ratio at that time,

7. Eliason, L. E.: *Nelson's Loose Leaf Surgery*, New York, T. Nelson & Son, 1927, vol. 3, p. 249.

but this was followed by a loss of strength which was only suggested in the roentgenogram. Thereafter, the agreement of the findings between the roentgenogram and the breaking strength became less. The rarefaction of the fragments was, however, readily seen as was the well healed fracture on the last two periods observed. The roentgenogram is of undoubted value, but considerable care must be exercised in attempts to interpret the strength of the callus from the picture seen.

The histologic studies in process of preparation on the healing fractures of animals on the different diets that we are using in our work calls for passing attention. These will be reported in a separate series of papers in the near future. An attempt will be made in these to correlate the breaking strength with the predominating cell response present on the different intervals.

SUMMARY

By use of an original beam testing machine, the breaking and healing strengths of normal and fractured fibulae of rats were studied. It was observed that:

1. The strength of the fibula of the rat was shown to be positively correlated with the fibular length and the animal weight. Similar correlations were shown to exist for any combination of these three variables.

2. The relation of body weight to fibular strength proved of considerable value. A formula to reduce the disparity in weights was developed. This resulted in the use of a breaking ratio R , as defined in the text.

3. The breaking strength of fifty pair of unfractured fibulae of normal normal rats on the standard diet one week had a ratio of 252 ± 9 for the left and 243 ± 9 for the right, respectively.

4. A series of standard control rats, free from fracture and on standard diet for from thirteen to fifty-two days, showed a breaking strength ratio which at times varied widely, but which fell steadily from the beginning to the end of the experiment.

5. There were found to exist simultaneously with the falling strength similar fluctuations in the animal weights and the quantitative food intake. As the one fell, the other fell, and as the one rose, the other likewise rose.

6. Similar correlations between animal weight, fibular length and fibular strength were seen to exist for this series of rats as for the normal normals.

7. A series of animals was kept on the standard diet for one week. Their right fibulae were then fractured. The rats were then killed at intervals of three days from the sixth to the forty-fifth days post-operatively, and the breaking strength ratios of the unfractured left fibulae and the healing strength ratios of the fractured right fibulae were determined. The ratio of the fractured right fibula rose sharply to the fifteenth day, by which time the primary callus had formed. The ratio fell from the fifteenth to the twenty-first days as the medullary cavity developed, and slowly rose by a process of cortical thickening and reorganization of the callus to equal the normal normal ratio on the forty-fifth day, when strength was considered to have been restored.

8. The ratios of the unfractured left fibulae closely followed the rises and falls in the ratios of the fractured right fibulae.

9. Again the animal weights and food intakes varied simultaneously with differences in the ratio from interval to interval.

10. Roentgenograms followed the healing strength ratios until the fifteenth day, after which the degree of density seen proved to be no indication of the true strength of the healing fibula.

11. The explanation of the comparatively close agreement between fluctuations in breaking or healing strength and animal weight and food intake is problematic. Several possibilities were considered, especially vitamins A and D, phosphatase, parathyroid hormone and the elaboration of a chemical substance at the fracture site.

CONCLUSIONS

1. The breaking strength ratio of the normal left fibula of the adult rat is 252 ± 9 , and of the right fibula 243 ± 9 .

2. A close correlation exists between body weight, fibular length and fibular strength in normal rats.

3. Normal fibular strength diminishes in rough proportion to the time the animal is on the standard diet (Moise and Smith).

4. The healing strength ratio of fractured right fibula of the rat rises with the formation of the primary callus, and falls with the development of the medullary cavity. Strength is restored to normal by the forty-fifth day through cortical thickening and reorganization of the callus.

5. Changes in the quantity of food consumed and the rats' weight exert a strong influence on both the healing and the normal breaking strength of the fibulae.

6. The roentgenogram is of distinct value in determining the fracture strength only up to the formation of the primary callus. Thereafter its value diminishes.

ADDENDA
COMPLETE DATA FOR STANDARD DIET

TABLE 2a.—Correlation Between Fibular Length and Fibular Strength in Normal Normal Rats

	2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right
	535	380	610	515	700	675	585	605
	525	370	600	620	535	480	770	800
	650	460	350	325	460	505	580	465
	560	480	320	350	490	445	465	700
	610	555	325	360	510	495	655	365
	190	205	455	435	525	510	550	620
	280	340	370	600	380	375	675	410
	360	300	355	400	365	360	390	380
	315	320	480	515	400	435	305	360
	410	290	595	500	455	385	310	400
	265	400	540	660	280	360	675	335
	330	300	325	375	420	420	320	305
	310	250	380	310				
Mean.....	411	358	441	459	460	454	523	495
Mean of left and right combined	384		450		457		509	

TABLE 3a.—Correlation Between Fibular Length and Animal Weight in Normal Normal Rats

2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.
236	250	290	300
234	250	284	300
216	240	282	294
212	242	273	290
210	240	263	290
210	238	252	290
210	232	246	286
203	230	235	286
202	220	228	280
201	220	224	278
200	200	200	272
195	200	240	238
192	230		
Mean	209	251	284

TABLE 4a.—Correlation Between Weight and Breaking Strength of Fibulae of Normal Normal Rats

190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
Left	Right	Left	Right	Left	Right	Left	Right
310	300	400	435	525	510	310	400
330	400	380	310	510	495	305	360
265	290	385	400	675	335	460	505
280	360	370	600	490	445	535	480
325	375	525	370			390	380
540	660	365	360			675	410
410	320	535	380			550	620
315	300	320	305			655	565
360	340	455	435			465	700
610	555	325	360			700	675
280	250	420	420			580	465
190	205	350	325			535	605
560	480	320	350			770	800
650	460	380	375				
595	500	600	620				
480	515	610	515				
455	385						
Mean.....	409	394	421	410	550	446	593
Combined mean	401		415		498		564

TABLE 6a.— $\frac{F}{10W^{2/3}} = R$ for Normal Rats Free from Fractures on Standard Diet

Rat No.	W	(10.w) ^{2/3}	F Left	F Right	R Left	R Right
2547.....	192	155	310	300	201	194
2274.....	195	156	330	400	211	256
2544.....	200	159	265	290	167	183
2263.....	200	159	280	360	176	227
2288.....	200	159	325	375	205	236
2265.....	200	159	540	660	340	416
2271.....	201	159	410	320	257	201
2548.....	202	160	315	300	197	188
2284.....	203	160	360	340	225	212
2257.....	210	164	610	555	372	338
2545.....	210	164	280	250	171	152
2546.....	210	164	190	205	116	125
2294.....	212	165	560	480	339	291
2252.....	216	167	650	460	380	275
2264.....	220	169	595	500	352	296
2270.....	220	169	480	515	284	305
2251.....	224	171	455	385	266	225
2281.....	228	173	400	435	231	251
2380.....	230	174	380	310	218	178
2551.....	230	174	385	400	221	230
2277.....	232	175	370	600	211	342
2276.....	234	176	525	370	298	210
2249.....	235	177	365	360	206	203
2262.....	236	177	535	380	302	214
2377.....	238	178	320	305	179	171
2275.....	238	178	455	435	255	244
2543.....	240	179	325	360	181	201
2378.....	240	179	420	420	234	234
2280.....	240	179	350	325	195	181
2285.....	242	180	320	350	177	194
2278.....	246	182	380	375	209	206
2282.....	250	184	600	620	326	337
2279.....	250	184	610	515	331	280
2247.....	252	185	525	510	283	275
2248.....	263	191	510	495	268	260
2250.....	272	195	675	335	346	172
2267.....	273	195	490	445	251	228
2287.....	278	198	310	400	157	202
2550.....	280	199	305	360	154	181
2259.....	282	200	460	505	203	253
2268.....	284	201	535	480	267	239
2260.....	286	202	390	380	194	189
2292.....	286	202	675	410	335	203
2272.....	290	203	550	620	270	305
2293.....	290	203	655	565	322	278
2255.....	290	203	465	700	229	344
2253.....	290	203	700	675	344	332
2266.....	294	205	580	465	283	227
2542.....	300	208	585	605	281	291
2549.....	300	208	770	800	370	385
Mean.....	243	177	458	440	252	243
Standard deviation mean	20	19	9	9

TABLE 7a.—*Ratios of Breaking Strength of Right and Left Fibulae of Standard Control Group*

Postopera- tive Days	Rat No.	W	(10.w) ^{2/3}	F for Left	F for Right	R for Left	R for Right
6	2737	262	190.1	650	625	341.9	328.7
	2475	285	205.7	670	675	325.7	328.1
	2738	265	191.5	575	590	300.2	308.1
	2739	254	186.2	675	580	362.5	311.4
						333 ± 11	319 ± 5
9	2389	300	208.0	525	575	252.4	276.4
	2390	300	208.0	470	560	226.0	269.2
	2391	284	200.6	640	440	319.0	219.3
	2415	244	181.2	400	360	220.7	198.6
						255 ± 20	241 ± 16
12	2424	220	169.1	250	220	147.8	130.1
	2425	228	173.2	290	285	167.4	164.5
	2747	250	184.2	490	560	266.0	304.0
	2748	250	184.2	630	690	342.0	374.5
						231 ± 39	244 ± 50
15	2420	210	164.0	280	265	170.7	161.5
	2421	216	167.1	320	340	191.5	203.4
	2742	198	157.7	295	300	187.1	190.2
	2423	225	171.7	330	325	192.1	189.2
						186 ± 4	186 ± 8
18	2743	194	155.6	300	260	192.8	167.1
	2417	196	156.6	275	285	175.6	182.0
	2418	230	174.2	300	320	172.2	183.7
	2419	232	175.2	280	250	159.3	142.7
						175 ± 6	169 ± 8
21	2428	295	205.7	495	380	240.6	184.7
	2429	216	167.1	260	255	155.5	152.6
	2430	210	164.0	340	260	207.3	158.5
	2431	280	198.6	515	460	258.8	231.6
						216 ± 20	182 ± 16
24	2385	290	203.4	655	625	322.0	307.2
	2386	280	198.6	630	675	317.9	339.8
	2387	220	169.1	350	350	206.9	206.9
	2388	300	208.0	605	570	290.8	274.0
						285 ± 23	282 ± 25
27	2381	235	176.8	410	380	231.9	214.9
	2382	210	164.0	310	300	189.0	182.9
	2383	260	189.1	790	775	417.7	409.8
	2744	260	189.1	450	375	238.5	198.3
						270 ± 43	252 ± 46
30	2377	238	178.3	320	305	179.4	171.0
	2378	240	179.3	420	420	234.4	234.4
	2379	236	177.3	345	390	194.5	220.0
	2380	230	174.2	380	310	218.1	177.9
						207 ± 10	201 ± 14
33	2373	225	171.7	200	225	116.4	131.0
	2374	208	162.9	320	310	196.4	190.2
	2375	210	164.0	185	200	112.7	121.9
	2376	296	206.2	365	340	177.0	164.9
						161 ± 18	152 ± 14
36	2369	267	192.5	275	260	142.8	132.4
	2476	232	175.2	425	400	242.5	228.3
	2371	207	162.4	300	280	184.7	172.4
	2372	200	158.8	285	225	179.4	141.6
						188 ± 18	169 ± 19
39	2365	222	170.2	315	280	185.0	170.3
	2366	292	204.3	440	400	215.3	195.8
	2367	212	165.0	350	350	230.0	212.0
	2368	285	201.0	445	440	221.4	218.9
						213 ± 13	199 ± 9
42	2361	245	181.7	365	390	200.8	214.7
	2362	220	169.1	325	290	192.2	171.5
	2363	300	208.0	575	590	276.4	283.6
	2364	232	175.2	385	410	219.8	234.0
						222 ± 16	226 ± 20
45	2340	235	176.8	500	475	282.8	268.6
	2341	300	208.0	505	485	242.8	233.1
	2342	230	174.2	225	220	129.1	126.0
	2458	300	208.0	505	485	242.8	233.1
						218 ± 12	209 ± 15

TABLE 8a.—Correlation Between Fibular Length and Strength in Standard Control Group

2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.		2.4 Cm.	
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
275	285	300	260	300	280	320	305	445	440
280	265	295	300	320	310	630	690	440	400
340	260	285	225	325	290	490	560	470	560
185	200	370	325	200	225	790	775	525	375
380	350	310	300	425	400	575	590		
320	340	260	255	325	350	275	260		
315	280	250	220	385	410	515	460		
350	350	375	360	410	380	630	675		
300	320	300	330	420	420	640	440		
330	325	290	285	365	390	670	675		
		225	220	675	580	655	625		
		500	475	650	625	385	350		
		350	310			495	380		
		290	255			365	340		
		280	250			505	485		
		345	390			575	590		
		400	360			605	570		
		245	260						
Mean	308	298	317	299	400	388	536	516	470
Combined mean	303		308		394		526		482

TABLE 9a.—Correlation Between Fibular Length and Animal Weight in the Standard Control Group

2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.	2.4 Cm.
195	194	207	238	286
210	198	208	250	292
210	200	222	250	300
210	206	225	260	300
214	210	232	265	
216	216	232	267	
218	220	232	280	
220	222	235	280	
222	225	240	284	
225	228	245	285	
	230	254	290	
	235	262	290	
	230		295	
	230		296	
	232		300	
	236		300	
	244		300	
	250			
Mean	214	223	233	278
				295

TABLE 10a.—Correlation Between Animal Weight and Fibular Strength in the Standard Control Group

190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
Left	Right	Left	Right	Left	Right	Left	Right
275	285	320	305	790	775	515	460
280	265	630	690	575	590	630	675
340	260	490	560	275	260	640	440
185	200	290	285	675	580	670	675
380	350	225	220	650	625	655	625
320	340	500	475			385	350
315	280	380	310			495	380
350	350	290	255			365	340
300	320	280	250			505	485
330	325	345	390			575	590
300	280	400	360			605	570
320	310	245	260			445	440
325	290	425	400			440	400
200	225	325	350			470	560
300	260	385	410			525	575
295	300	410	380				
285	225	420	420				
370	325	365	390				
310	300						
260	255						
250	220						
375	360						
300	330						
Mean	303	289	373	373	593	566	528
Combined mean	296		373		580		504
							516

TABLE 11a.—*Data on Weight and Food in Standard Control Group*

Postoperative Days	Rat No.	Weight			Food Consumed		
		Start	Operation	Death	Start to Operation	Operation to Death	
6	2475	275	285	276	90	80	
	2737	260	262	254	65	44	
	2738	260	265	258	71	47	
	2739	258	254	255	70	67	
			267	261	74	60	-6
9	2390	295	300	315	70	111	
	2391	272	284	280	50	78	
	2415	236	244	250	86	65	
	2389	300	300	330	105	122	
			282	294	78	94	+12
12	2424	220	220	226	101	67	
	2425	212	228	228	107	80	
	2747	260	250	230	49	86	
	2748	258	250	220	72	150	
			237	226	82	96	-11
15	2420	215	210	200	79	100	
	2421	212	216	210	88	94	
	2423	220	225	218	80	88	
	2742	210	198	186	48	138	
			212	204	74	105	-8
18	2417	196	195	195	76	141	
	2418	230	222	194	80	166	
	2419	232	232	225	70	156	
	2743	198	194	170	50	161	
			211	196	69	131	-15
21	2428	290	295	276	74	214	
	2429	215	216	178	56	176	
	2430	200	210	210	85	129	
	2431	270	280	262	82	202	
			250	232	74	180	-18
24	2385	280	290	220	112	228	
	2386	272	280	240	67	230	
	2387	210	220	210	67	200	
	2388	300	300	258	77	233	
			273	232	81	223	-41
27	2381	235	235	230	65	182	
	2382	210	210	192	67	199	
	2383	250	260	238	70	235	
	2744	260	260	186	59	194	
			241	212	65	203	-29
30	2377	245	238	225	57	202	
	2378	225	240	222	73	224	
	2379	230	236	218	57	160	
	2380	225	230	220	52	238	
			236	221	60	206	-15
33	2373	225	225	190	58	214	
	2374	220	208	208	54	226	
	2375	210	210	160	45	170	
	2376	285	296	260	95	307	
			235	205	63	229	-30
36	2476	230	232	200	80	355	
	2369	268	267	218	78	236	
	2371	206	207	190	52	273	
	2372	196	200	196	54	241	
			227	201	66	276	-26
39	2365	210	218	194	69	270	
	2366	294	292	248	86	309	
	2367	214	214	206	64	257	
	2368	286	286	250	80	322	
			253	225	75	290	-25
42	2361	255	245	208	58	310	
	2362	220	222	180	53	276	
	2363	300	300	234	94	371	
	2364	235	232	220	63	298	
			252	211	67	314	-41
45	2340	245	235	198	83	314	
	2341	300	300	226	93	363	
	2342	215	230	199	83	288	
			255	208	86	322	-47

TABLE 11a.—Data on Weight and Food in Standard Control Group—Continued
(Summary)

Post-operative Days	Weight at Operation, Gm.	Difference in Weight From Operation to Death, Gm.	Food Consumed per Day From Operation to Death, Gm.	Difference in Weight From Operation to Death as per Cent of Weight at Operation	Food Consumed From Operation to Death per Day as per Cent of Weight at Operation
6	267	— 6	10.0	— 2.25	3.75
9	282	—12	10.4	— 4.25	3.33
12	237	—11	8.0	— 4.64	3.37
15	212	— 8	7.0	— 3.77	3.30
18	211	—15	7.3	— 7.11	3.46
21	250	—18	8.6	— 7.20	3.44
24	273	—41	9.2	—15.02	3.43
27	241	—20	7.5	—12.03	3.11
30	236	—15	6.9	— 6.35	2.92
33	235	—30	6.9	—12.76	2.93
36	227	—26	7.7	—11.45	3.39
39	253	—28	7.4	—11.06	2.92
42	252	—41	7.5	—16.27	2.99
45	255	—47	7.2	—18.39	2.82

TABLE 12a.—Breaking Strength Ratios in Standard Group with Fracture

Post-operative Days	Rat No.	Weight (W)		Force (F)		Ratio (R)	
		At Operation	(10.w) ^{2/3}	Left	Right	Left	Right
6	2299	196	156.6	260	55	166	55
	2300	232	175.2	310	0	177	0
	2302	220	169.1	305	40	180	24
	2343	280	198.6	440	0	222	0
	2344	237	177.8	340	75	191	42
		250	184.2	750	80	407	43
		226	172.2	730	140	424	81
		220	169.1	590	50	349	30
		230	174.2	460	75	264	43
	Arithmetic mean.....					264	33
	Standard deviation mean.....					±32	±8
9	2313	255	186.7	600	415	321	222
	2316	244	181.2	670	170	370	94
	2317	238	178.3	510	340	286	191
	2318	225	171.7	610	340	355	198
	2326	243	180.8	435	185	241	102
		215	166.6	243	55	146	33
		295	205.7	465	80	226	39
		190	153.4	280	195	183	127
		205	161.4	370	170	229	105
	Arithmetic mean.....					262	124
	Standard deviation mean.....					±24	±21
12	2241	222	170.2	405	395	238	232
	2242	264	191.0	710	430	372	225
	2243	290	203.4	650	400	320	197
	2244	250	184.2	480	405	261	220
	2245	225	171.7	355	100	207	58
		263	192.9	720	390	373	202
		270	193.9	580	275	299	142
		200	158.8	330	210	208	132
		255	186.7	470	110	252	59
		213	165.6	345	110	208	66
	Arithmetic mean.....					274	153
	Standard deviation mean.....					±20	±22
15	2233	264	191.0	540	355	283	186
	2234	280	198.6	600	445	302	224
	2235	276	196.8	605	375	307	191
	2236	235	201.0	550	395	274	192
	2239	290	203.4	560	555	275	273
		200	158.8	540	360	340	227
		275	196.3	980	320	500	163
Arithmetic mean.....						326	208
Standard deviation mean.....						±29	±13

TABLE 12a.—*Breaking Strength Ratios in Standard Group with Fracture*
—Continued.

Post-operative Days	Rat No.	Weight (W)		Force (F)		Ratio (R)	
		At Operation	(10.w) ^{2/3}	Left	Right	Left	Right
18	2228	289	202.9	340	330	168	163
	2229	300	208.0	540	105	260	51
	2230	300	208.0	450	410	216	197
		222	170.2	310	280	182	165
		263	190.5	610	510	320	268
		195	156.1	310	275	198	183
		230	174.2	425	115	250	66
	Arithmetic mean.....					228	156
	Standard deviation mean.....					±19	±26
21	2541	300	208.0	650	295	313	142
	2539	290	203.4	265	170	130	84
	2537	273	195.3	195	375	100	192
	2534	240	179.3	405	400	226	223
	2538	285	201.0	340	180	169	90
	2540	290	203.4	300	325	147	160
	2535	190	153.4	250	115	163	75
	2536	192	154.5	200	90	129	58
	Arithmetic mean.....					172	128
	Standard deviation mean.....					±21	±19
24	2145	300	208.0	570	70	274	33
	2147	265	191.5	240	150	125	78
		300	208.0	485	390	233	188
		225	171.7	240	260	140	152
		212	165.0	295	250	179	152
		235	176.8	555	260	314	147
		300	208.0	890	415	428	200
		232	178.0	310	320	177	183
	Arithmetic mean.....					334	205
	Standard deviation mean.....					245	149
						±32	±18
27	2136	284	200.6	410	180	204	90
	2140	218	168.1	325	300	193	178
		215	166.6	285	140	171	84
		220	169.1	385	325	228	192
		196	156.6	225	230	144	147
		224	171.2	880	540	515	315
	Arithmetic mean.....					243	168
	Standard deviation mean.....					±50	±31
30	2127	220	169.1	315	190	186	113
	2128	210	164.0	275	160	168	98
	2130	285	201.0	425	395	212	197
	2131	230	174.2	215	...	123	...
	2133	278	197.7	425	220	215	111
		220	169.1	355	425	210	231
		258	188.1	490	560	261	298
		215	166.6	465	165	279	99
	Arithmetic mean.....					207	167
	Standard deviation mean.....					±16	±29
33	240	179.3	425	300	237	167
		272	194.9	440	...	226	...
		215	166.6	290	210	174	126
		275	196.3	390	400	198	204
		220	169.1	310	...	183	...
		255	186.7	330	210	177	112
		300	208.0	690	290	332	159
		250	184.2	435	360	236	195
	Arithmetic mean.....					220	157
	Standard deviation mean.....					±17	±14
36	2478	260	189.1	615	330	325	174
	2479	275	196.3	565	375	287	191
	2480	285	201.0	495	425	246	211
	2481	300	208.0	585	330	257	159
	2482	263	190.5	485	305	255	160
	Arithmetic mean.....					274	179
	Standard deviation mean.....					±13	±9

TABLE 12a.—*Breaking Strength Ratios in Standard Group with Fracture*
—Continued

Post-operative Days	Rat No.	Weight (W)		Force (F)		Ratio (R)	
		At Operation	(10.w) ^{2/3}	Left	Right	Left	Right
39	2109	265	191.5	415	250	217	131
		210	164.0	445	250	271	171
		274	195.8	740	395	327	201
		218	168.1	480	270	286	161
		254	186.2	660	390	354	210
		200	158.8	370	435	233	273
		204	160.9	600	425	373	264
		Arithmetic mean.....					294
		Standard deviation mean.....					±20
							±19
42	2099	250	184.2	360	385	196	209
		224	171.2	340	190	199	111
		202	159.8	460	330	288	207
		218	168.1	300	330	174	196
		205	161.4	370	320	230	195
		Arithmetic mean.....					217
		Standard deviation mean.....					±18
							±17
45	2093	200	158.8	385	350	242	220
		220	169.1	480	575	284	340
		2094	171.2	340	275	191	158
		2097	173.7	340	275	191	158
		260	189.1	415	440	219	233
		190	153.4	295	425	192	277
		224	171.2	380	370	222	216
		235	176.8	815	650	461	368
		230	174.2	590	440	339	253
		Arithmetic mean.....					269
		Standard deviation mean.....					±31
							±23

TABLE 13a.—*Body Weight and Food Intake of Rats in the Combined Group with Fracture*

Post-operative Days	Rat No.	Body Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
6	2299	200	196	190	60	37
	2300	232	232	226	57	38
	2302	210	220	225	90	57
	2343	280	280	275	63	41
	2344	227	237	235	74	48
	250	268	..	85
	236	232	..	62
	220	225	..	73
	230	230	..	87
	Mean.....	230	232	234	69	59
9	2313	278	255	284	72	113
	2316	268	244	235	24	49
	2317	255	238	212	56	52
	2318	252	225	240	50	124
	2326	218	243	255	68	106
	215	220	..	49
	295	290	..	70
	190	190	..	69
	205	190	..	50
	Mean.....	254	234	235	54	76
12	2241	228	222	224	62	95
	2242	265	264	259	65	174
	2243	285	290	292	71	114
	2244	265	250	261	60	113
	2245	222	225	212	72	81
	268	280	..	150
	270	299	..	132
	200	210	..	90
	255	262	..	125
	213	205	..	93
	Mean.....	253	246	253	66	117

TABLE 13a.—*Body Weight and Food Intake of Rats in the Combined Group with Fracture—Continued*

Post-operative Days	Rat No.	Body Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
15	2233	268	264	285	76	152
	2234	278	280	280	139	256
	2235	270	276	260	106	144
	2236	278	285	294	84	227
	2239	288	290	296	129	155
	200	220	...	138
	275	280	...	158
Mean.....		276	267	274	107	176
18	2228	288	289	260	85	170
	2229	285	300	298	96	226
	2230	292	300	265	85	121
	222	250	..	149
	263	280	..	180
	195	192	..	132
	230	230	..	119
Mean.....		288	257	258	89	158
21	2534	245	240	240	55	160
	2535	195	190	196	20	123
	2536	212	192	190	35	165
	2537	275	273	250	61	184
	2538	280	285	275	85	156
	2539	278	290	265	90	210
	2540	280	290	265	86	175
Mean.....		257	258	246	76	142
24	2145	292	300	288	92	308
	2147	245	265	270	85	231
	235	268	..	276
	232	248	..	250
	200	252	..	300
	300	362	..	300
	225	180	..	164
Mean.....		...	212	170	..	145
		...	300	305	..	195
		269	252	260	89	241
27	2136	275	284	275	104	255
	2140	212	218	215	131	227
	215	210	...	178
	220	255	...	232
	196	190	...	141
	224	268	...	283
	219
Mean.....		244	226	236	118	
30	2127	222	220	215	78	305
	2128	202	210	204	105	285
	2130	270	285	266	96	321
	2131	222	230	218	130	323
	2133	260	278	285	100	338
	220	278	...	358
	215	280	...	372
Mean.....		...	258	318	...	360
		235	240	258	103	333
33	2113	230	240	225	96	344
	2116	246	272	235	95	397
	2117	215	215	190	62	265
	2118	255	275	245	95	435
	2119	200	220	193	93	357
	255	268	..	264
	250	280	..	268
Mean.....		...	300	308	..	281
		229	253	243	88	339
36	2478	250	260	225	68	272
	2479	270	275	230	74	251
	2480	290	285	225	60	234
	2481	290	300	270	84	251
	2482	260	263	220	84	270
Mean.....		272	277	234	74	292

TABLE 13a.—*Body Weight and Food Intake of Rats in the Combined Group with Fracture—Continued*

Post-operative Days	Rat No.	Body Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
39	2109	256	265	252	95	359
		...	210	240	..	331
		...	274	289	..	372
		...	218	235	..	306
		...	254	300	..	417
		...	260	285	..	390
		...	204	270	..	466
		Mean.....	256	232	267	95
42	2099	230	250	226	83	367
	2104	218	224	190	85	351
	202	230	..	303
	218	225	..	333
	205	200	..	299
	Mean.....	224	220	214	84	331
45	2093	205	200	196	56	369
	2094	200	220	226	73	419
	2097	200	229	196	106	336
	260	290	...	405
	190	208	...	357
	224	231	...	313
	235	290	...	556
	230	232	...	379
	Mean.....	202	224	234	78	392

FRACTURES OF THE LOWER RADIAL EPIPHYSIS *

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In 1898, J. Poland very completely and thoroughly discussed traumatic separations of the lower radial epiphyses. Eight years later two masterly treatises dealing entirely with injuries to the lower radial epiphysis appeared in the Paris Theses: one by Metenier and the other by Bonta. Not until 1922 and 1924, with the reports of M. K. Smith, does this subject again attract attention in the literature.

ANATOMY

The lesion dealt with here is one in which there is a solution of continuity in the radius at its lower extremity, and all, or at least part, of the line of separation passes through the cartilaginous plate of the epiphysis. The resultant condition fulfils the requirements of, and should be called, a fracture instead of a separation or dislocation.

One knows that the longitudinal growth of a long bone is due to a proliferation of the tissue at and adjoining the epiphyseal cartilage, and the proliferating cartilaginous cells depend for their activity on their blood supply. The epiphysis obtains its blood supply from the periosteal network of arteries, large branches of which perforate the thin layer of compact tissue on its exterior and are distributed throughout the spongy cancellous tissue. Nearly the whole of the blood supply is therefore independent of the diaphysis. Only one or two minute arteries pass from the diaphysis through the conjugal cartilage into the epiphysis. This accounts for the comparatively infrequent occurrence of necrosis of the epiphysis in traumatic separation of the epiphysis even when the diaphysis is more or less completely displaced from the epiphysis. The periosteum covering the diaphysis is less adherent than that covering the epiphysis and is more easily stripped up as a result of trauma. The epiphysis toward which the nutrient artery points usually unites to the shaft first, and consequently the greater longitudinal growth is produced by the opposite epiphysis. The lower radial and ulnar epiphyses unite later than the upper ones do, and so produce the greater longitudinal growth. The synovial pouch of the carpus is in contact with the lower radial epiphysis only on its medial surface, and is rarely lacerated in fractures of the epiphysis. There are no important muscular or fibrous attachments to the lower radial epiphysis.

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* From the Fifth Avenue Hospital.

In the common posterior displacement noted in lower radial epiphyseal fractures, the following changes in the normal anatomy are noted:

- 1. The periosteum is torn through on the anterior aspect at the level of the conjugal cartilage and stripped up on the dorsal aspect.
- 2. The line of separation is smooth. There are no spicules of bone to interlock and hold the fragments separated.
- 3. A few fibers of the pronator quadratus muscle are lacerated.
- 4. Cases of radial or median nerve involvement have been reported.
- 5. The cells of the cartilaginous plate are more or less damaged.
- 6. The periosteal and nutrient artery blood supply is interfered with.

S. L. Haas, in his work on epiphyseal transplantation, stated that the epiphysis was a highly specialized tissue very much dependent on

Age at Which Epiphyseal Ossification Occurs in the Lower Radius and Ulna*

		Radius		Ulna	
		Proximal	Distal	Proximal	Distal
1911	Byree.....	17-19	18-20	17-19	18-20
1912	Dixon.....	18	21-25	17	20
1911	Dwight.....	16	19-20	16	18
1892	Gegenbaur.....	17	20	17	20
1871	Henle.....	16	19-20	15-16	20
1909	Krause.....	16-17	20-21	16-17	20-21
1918	Lewis.....	17-18	20	16	20
1911	Poirier.....	16-19	20-25	20-21	22-24
1921	Terry.....	17	20	16-17	18-20
1921	Testal.....	16-20	20-25	16-20	20-25
1921	Thompson.....	18-20	20-25	16	20-23
Earliest.....		16	18	15	18
Latest.....		20	25	21	25
Difference.....		4	7	6	7

* From Stevenson (Am. J. Phys. Anthropol., January-March, 1924, vol. 7, no. 1).

its blood supply and, for this reason, a very vulnerable tissue with its viability after transplantation directly dependent on its blood supply.

The age at which epiphyseal ossification takes place in the lower radius and ulna has been variously reported. The accompanying table by Stevenson gives the ages and the authority from which each is quoted. The average is 18 years for the head of the radius, from 16 to 17 years for the head of the ulna, and 19 years for both distal epiphyses.

INCIDENCE

Fracture of the lower radial epiphysis is the most common of all the epiphyseal fractures, and, according to Poland, this frequency is due in all probability to the following facts: (1) its anatomic characteristics (it is large in comparison with its adjacent diaphysis and

it has a superficial location); (2) its skeletal situation is such that it is subject to indirect violence through trauma to the carpus and hand; (3) the lower radial epiphysis does not diminish in size in relation to the rest of the growing bone as do the epiphyses of other long bones; (4) this epiphysis is one of the last to become ossified to its diaphysis, and so it is potentially exposed to the possibility of fracture over a longer period of time, and (5) it is possible that because of its superficial location the diagnosis is less often missed than is the case with epiphyses in less accessible locations.

In 1878 Bruns reported a series of eighty-one cases with 101 fractures at or near the epiphysis, and the most frequent site was the lower end of the femur (twenty-eight cases) and next the lower end of the radius (twenty-five cases). However, his work was recorded before the use of x-rays for diagnosis. Later reports show that the lower radial epiphysis is most frequently fractured.

Age.—It is well known that the majority of cases are seen in the second decade of life. Poland gives a series of twenty-eight cases, and twenty-three of these patients were between the ages of 12 and 18. There were five patients under 9 years of age, one of these an infant aged 1 year. M. K. Smith reported twelve cases in patients with an average age of 14 years. The injury is relatively uncommon after 18 years of age.

In 1834, Dupuytren first pointed out that when a child fell on the outstretched hand, a fracture of the forearm resulted and not a fracture of the lower end of the radius as in an adult. Coulon, in his work, "Fractures in Children," made the same statement, adding that when an epiphyseal fracture does occur, it is usually in children 13 or 14 years of age and rarely before the age of 10 years. The epiphysis is relatively more resistant to trauma than the lower end of the radius in adult life. The majority of the patients are of the male sex; 80 per cent of Poland's cases were in boys.

ETIOLOGY AND TREATMENT

Etiology.—A back thrust from a fall on the outstretched hand or from hyperextension, as from a back-firing motor, are the usual causes, or, as Cotton said, the causes are the same as those which produce a Colles' type of fracture in the adult; he added that they occur more often in grown boys than in small children. These fractures are nearly always due to indirect violence, as in falls from a height on an outstretched and pronated hand when the weight of the body is transmitted through the ball of the thumb to the posterior part of the radial epiphysis, causing the fracture and the backward displacement of the lower fragment, as is most commonly the case. A direct crush-

ing blow at the site of the epiphysis may readily produce the fracture, but is an uncommon cause.

Diagnosis.—The displacement of the lower radial epiphysis is usually upward and backward. It is diagnosed by the resulting dinner-fork deformity together with increased anteroposterior diameter, limitation of flexion and extension, and radial deviation; also by pain and point tenderness on pressure over the epiphyseal line. Impaction is rare. Roentgenograms of the normal as well as the injured wrist should be taken in the anteroposterior and lateral directions. It is well to note that epiphyseal fractures without displacement often cannot be picked up by roentgenography and are commonly diagnosed as "sprains." Unfortunately these undiagnosed fractures are prone to result in arrest of growth. Forward displacement of the epiphysis is not uncommon and gives a clinical picture similar to the "reversed Colles' fracture" of adult life. An accompanying fracture of the styloid process of the ulna is not uncommon. A soft crepitus may be made out, but it is not necessary for diagnosis and should not be sought for.

Treatment.—When there is no displacement, or after reduction of a slight displacement (which can be done readily without an anesthetic), the hand and forearm are put up in a simple retentive splint for from eighteen to twenty days. Complete displacements should be reduced under an anesthetic by hyperextension, traction and flexion manipulation. There is little tendency for the deformity to recur after complete reduction. The union is more rapid than in Colles' fractures in adults. In complicated cases, an open operation may be necessary. Poland collected four cases in which it was necessary to resect the diaphyseal end of the radius to effect the reduction of the fragments. He mentioned the necessity for resection of the whole or part of the injured radial epiphysis in some cases in which the epiphysis was severely comminuted or when ankylosis appeared certain. He also stated that conjugal chondrectomy, that is, excision of the conjugal cartilage of the ulna, may be performed to produce its arrest of growth in deformity arising from cessation of growth of the radius after epiphyseal injury. This is especially desirable when there is still a considerable period of time before the bone reaches its limit of increase in length.

J. Walton stated that if there is subsequent cessation of growth of the radius after epiphyseal injury, it may be necessary to remove a section of the shaft of the ulna to overcome the resulting deformity of the wrist.

I. Zadek believed that in fractures of the lower radial epiphysis, as against Colles' fractures, there are two smooth surfaces in contact and an absence of interlocking spicules of bone to help maintain the

reduction, and that with the usual upward and backward displacement of the epiphysis of the radius, the epiphysis may be forced into place readily, but there is a strong tendency for the displacement to recur immediately. He recommended a general anesthetic for reduction with maintenance by means of a circular plaster of paris cast with the wrist in 100 degrees palmar flexion for two and one-half to three weeks.

Complications.—Besides the separation of the lower fragment, there may be another fracture line through the epiphysis, or the epiphysis may be severely comminuted although the structure is more resistant than the corresponding portion of the radius in adult life. Laceration of the muscle fibers of the pronator quadratus is mentioned, but only a few fibers are attached to the epiphysis and this complication is unimportant. If the fracture is limited to the epiphysis the wrist joint will always escape injury. However, traumatic arthritis in the wrist may be produced by the exciting cause. The periosteum of the lower diaphysis is usually detached or lacerated and a bit of it may become wedged between the fragments. Accompanying the radial lesion, there may be a fracture of the ulna styloid, but this is not as common as in Colles' fractures. A fracture of the adjacent shaft of the radius frequently occurs. Cases of pressure on the radial and median nerve have been reported. The most important, and not the least frequent, complication arising after an epiphyseal fracture is a disturbance in growth activity. The severity of the resulting deformity is dependent on the degree of injury to the epiphyseal cartilage and its blood supply. Minor injuries to these structures cause retardation of longitudinal growth and more severe injuries produce a premature ossification of the epiphysis to the diaphysis, the resulting degree of wrist deformity being greater the younger the patient is at the time of the accident.

Prognosis.—No cases of non-union have been reported, and, in the uncomplicated cases, union takes place in the second or third week. The resulting wrist function is good. Deformity is usually due to nonreduction or union in a faulty position, and this deformity is usually completely effaced in following years. Arrest of growth causes marked deformity because of the increase in length of the adjacent ulna. DePaoli did not find any evidence of arrested growth after two years in any of his seventeen cases. J. Poland collected eighteen cases of arrested growth. M. K. Smith had twelve cases five of which showed retardation of growth, and of these three had premature ossification. He stated that the prognosis should be guarded because it depends on four factors: (1) the roentgen appearance, (2) the extent of the injury, (3) the reduction and (4) the age of the patient.

E. W. Andrews reported on the medicolegal aspect of premature ossification. He looked up the literature in defense of a fellow practitioner who was being sued for malpractice because of a fracture which

he had apparently adequately reduced when the patient was a child. The patient had developed a marked deformity in later life due to premature ossification of the radial epiphysis.

The literature contains very few references to the treatment for premature ossification of the lower radial epiphysis. Conjugal chondrectomy and osteotomy of the ulna are mentioned as possibilities, but the indications for, and the results of these operations were not mentioned. For this reason it seems worth while to report two cases, in one of which an operation was performed, and in the other no operation, with a follow-up of each.

REPORT OF CASES

CASE 1.—W. F., a boy, aged 12 years, came to the outpatient department of the Fifth Avenue Hospital on Sept. 19, 1929, complaining of weakness and deformity of the left wrist of six years' duration. Seven years previously, when he was 5 years old, he fell from a height of 10 feet (3 meters) into a basement, striking his head and left arm. He was taken to a city hospital. The report from that institution follows:

W. F., a white 5 year old boy, was admitted to the hospital on July 5, 1923, and was discharged on July 7. The diagnosis was a fractured left radius.

History.—The patient was brought to the hospital in a taxicab, and his father stated that he fell about 10 feet, striking on both hands. He got up and ran home, which was about a block away from the accident. He said that his left hand hurt him and he could not use it.

Examination.—There was an abrasion about 2 inches (4.6 cm.) in diameter on his forehead. His upper lip was markedly swollen and there was ecchymosis about both eyes. Dry blood was noted in both nostrils. The pupils were equal but slightly dilated. The left wrist showed the usual appearance of a Colles' fracture. The chest and abdomen were normal.

Diagnosis.—A provisional diagnosis of fractured skull, concussion of the brain and left Colles' fracture was made, and roentgenograms taken of the left forearm showed an oblique fracture through the lower left radial epiphysis *with no displacement*. Roentgenograms of the skull showed no evidence of fracture.

Treatment.—An anterior molded splint was applied, and the patient was put to bed. His pulse was taken every hour, showing a rate of between 100 and 110. His temperature remained normal and he was conscious all the time and took nourishment well. He remained in the hospital for two days and was then taken home. After two weeks the splint was removed and his condition was considered satisfactory.

Subsequent History.—For the first year or two after the accident, there was no apparent difficulty with the left wrist. Then the mother noted a very slight deformity which slowly became more noticeable up to one year ago, when it was quite obvious that something was wrong. During the past year the deformity rapidly became more pronounced, and the patient began to complain of weakness in his left hand. In August, 1929, he went to another hospital where roentgenograms were taken and the old fracture was recognized. Considerable deformity of the left wrist was present at that time. He was advised to return for observation

over a period of months to determine the extent of the epiphyseal injury. This he did not do, and the following month he was admitted to the Fifth Avenue Hospital.

Physical Examination.—The general appearance was that of a husky boy of 12 years. The routine examination gave negative results except for the local condition. The results of laboratory examinations were negative. Local condition: The left forearm as well as the left hand was smaller than the right. The left forearm was $1\frac{3}{4}$ inches (3.3 cm.) shorter than the right as measured from the olecranon to the tip of the middle finger. The musculature of the left hand and forearm was less well developed than that of the right, and the left hand showed a marked radial deviation. The lower end of the ulna protruded downward and outward. The left grip was weaker than the right. Ulnar deviation was limited while radial deviation was increased. Pronation and supination were not limited,

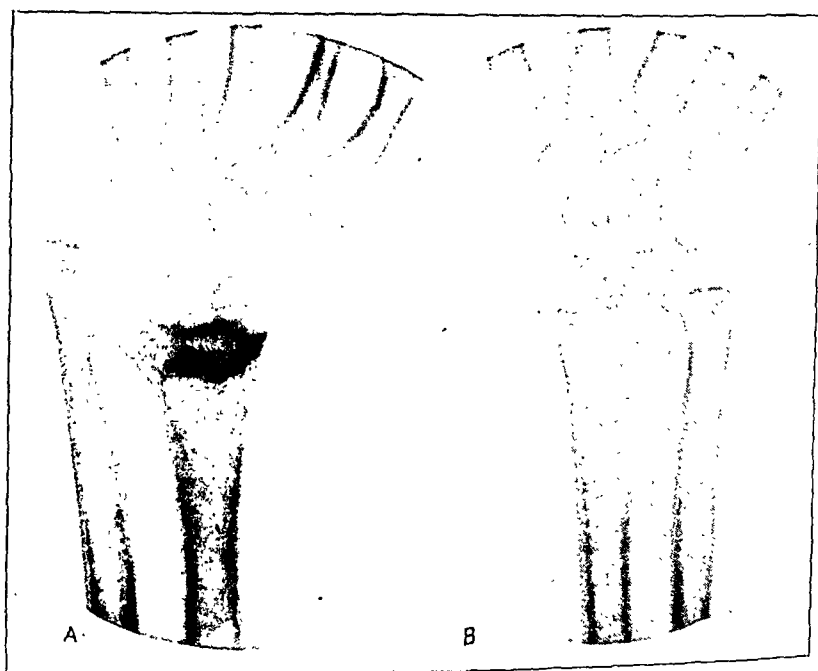


Fig. 1.—*A*, roentgen appearance of the injured wrist in case 1, six years after the accident. It shows the premature ossification of the lower radial epiphysis and the increase in ulnar length; also the radial deviation deformity. *B*, the normal wrist.

and flexion and extension were only slightly limited by weakness. The radio-ulnar attachments were loose and allowed free up and down movement of either bone. The lower end of the radius presented a roughened, irregularly prominent, bony thickening.

A provisional diagnosis of old injury to the lower radial epiphysis with retardation of growth was made.

Roentgen examination (fig. 1 *A*) showed an old fracture through the lower end of the radius which was apparently markedly impacted. The lower end of the radius was spread outward and cupped. The epiphysis had been destroyed or at least rendered inactive as the ulna had lengthened, so that the styloid process was approximately three fourths of an inch (1.90 cm.) lower than the articular surface of the lower end of the radius, thus causing deviation of the carpus toward

the radial side of the forearm. Roentgen measurements showed the left ulna to be 18.5 cm. in length and the right 20.5 cm.; the left radius, 14.75 cm., and the right 19.75 cm.

The patient was admitted to the hospital on Sept. 23, 1929, and discharged on October 26. On September 27, under general anesthesia, a 2 inch (5.08 cm.)

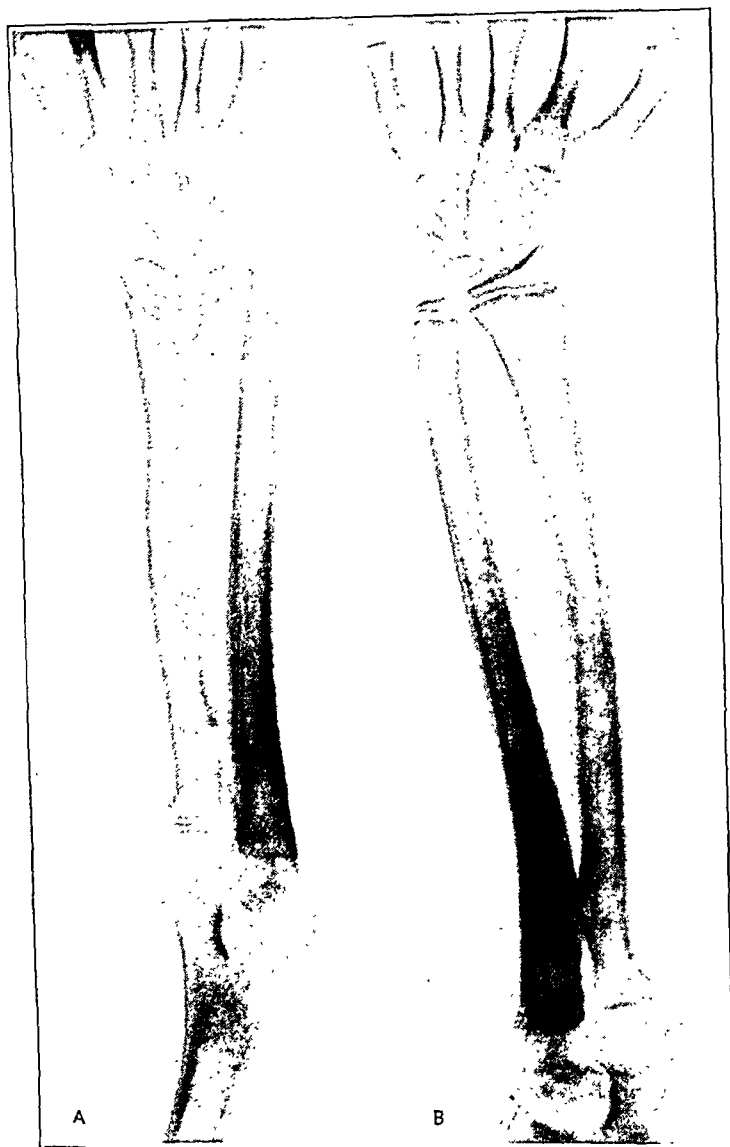


Fig. 2.—*A*, the periosteal thickening about the amputated end of the ulna. *B*, roentgenogram of the normal forearm and wrist showing the greater length as compared with side on which the operation was performed.

longitudinal incision was made medial to the distal end of the left ulna. At a point judged to be at the level of the lower radial articulation the ulna was cut through with a Gigli saw and the lower fragment excised. A few thinned-out fibers of the pronator quadratus were stripped from the lateral surface. No nerves or large blood vessels were cut. The wound was closed without drainage, and

anterior and posterior molded plaster of paris splints were applied with the hand in the cock up position and ulnar deviation. The patient was examined roentgenologically on leaving the operating room, and the following report was made: "Films of the left wrist show that the lower end of the ulna has been removed so that its lower margin is about on a level with the lowest point of the articular surface of the radius."

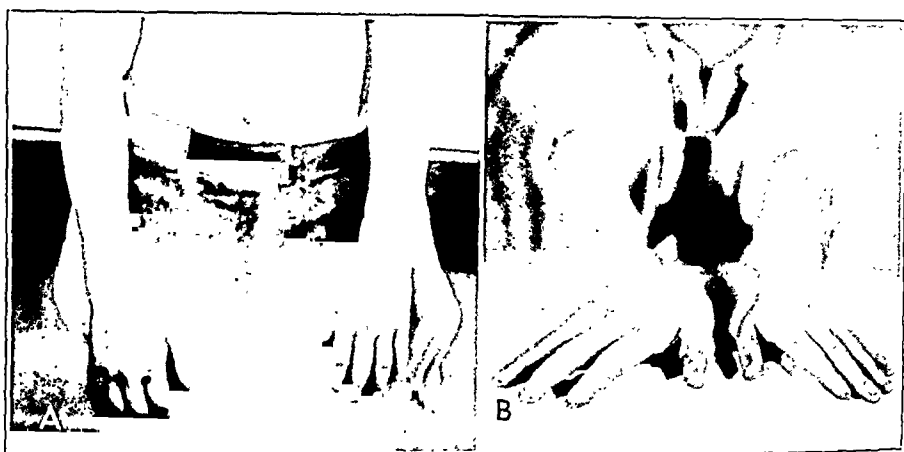


Fig. 3.—*A*, postoperative appearance, showing the shortening of the left forearm. *B*, photograph showing the ulnar deviation of the left wrist practically equal to that of the right wrist.

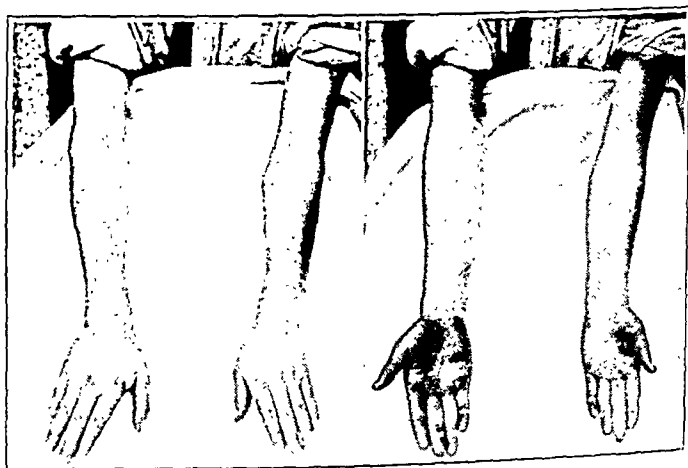


Fig. 4.—Appearance of the arm fifteen months after operation.

Postoperative Course.—The wound healed by primary union, and, except for a small blister on the anterior surface of the wrist due either to iodine or to the closely applied splints and a slight, temporary, unexplained rise in temperature on the seventeenth postoperative day, the patient made an uneventful recovery. Chest films taken during the temperature elevation were negative for lung involvement. The splints were discarded on the twelfth postoperative day, and exercises, baking and massage were started.

Pathologic examination of the excised epiphysis was not done because it was apparently normal. The patient was discharged from the hospital on the twenty-ninth postoperative day.

Follow-Up Examination.—One month after the operation, the patient's wrist motion was good and there was a decided increase in the degree of ulnar deviation

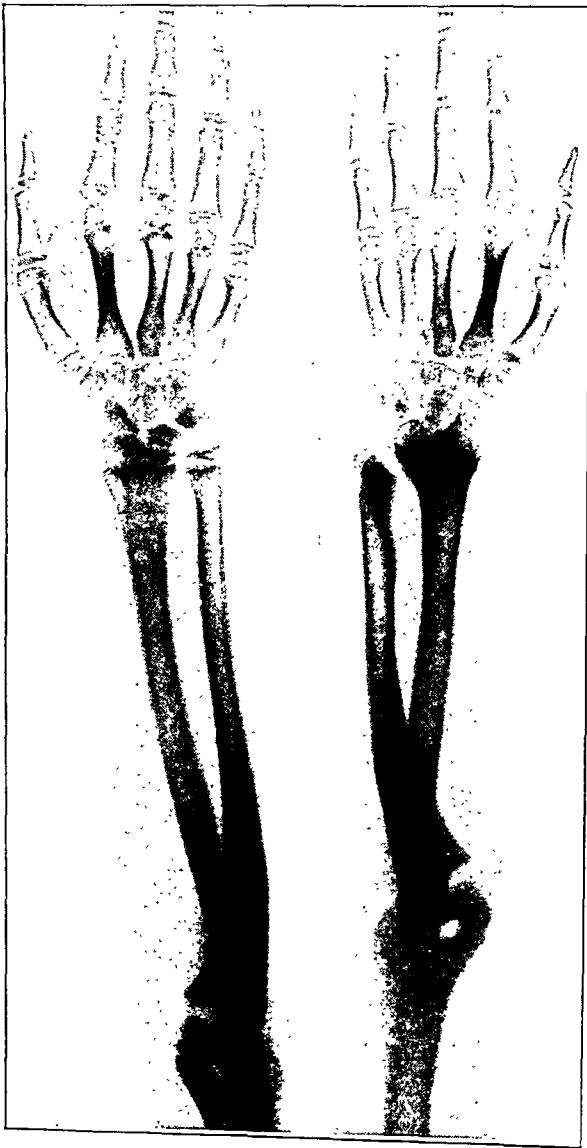


Fig. 5.—Roentgen appearance of both arms fifteen months after operation.

and wrist strength. A conspicuous, firm, thickening about the lower end of the ulna was noted and a roentgenogram (fig. 2 A) taken at that time showed a smoothed lower ulnar surface and a periosteal thickening. Pronation and supination were considerably limited because of the periosteal reaction at the lower end of the ulna. The general appearance of the left arm as compared with the right is shown by the photographs (fig. 3) taken at this time.

Ten weeks after operation the following measurements were taken:

	Left, Cm.	Right, Cm.
Circumference of wrist.....	15.0	14.0
Length from olecranon to tip of middle finger.....	33.0	37.5
Circumference at level of metacarpophalangeal joint.....	15.5	17.5
Circumference of forearm.....	17.5	18.5
Circumference at elbow.....	19.5	21.0
Length of radius (roentgenogram).....	14.7	19.7
Length of ulna before operation (roentgenogram).....	18.5	20.5
Length of ulna after operation (roentgenogram).....	16.7	20.5



Fig. 6.—The deformity in case 2, resulting from premature ossification of the lower radial epiphysis.

Five months after the operation the left wrist showed good function and strength, ulnar deviation being only slightly limited. Fifteen months after the operation there was practically no limitation of strength or mobility in the left wrist; the patient was playing basket ball and had even engaged in several fist fights with considerable success.

CASE 2.—J. R., a man, 38 years old, an Italian, came into the hospital for resection of a growth in the large bowel. A deformity of the left forearm was noted and the following typical history was obtained:

At the age of 5 years he was sliding down a banister when he fell, landing three flights below. He was unconscious when picked up and was suffering from a lacerated scalp and fractured left forearm and knee. He was treated in his home where he remained in bed for one month. During that time four attempts



Fig. 7.—Roentgen appearance of both forearms in case 2.

were made to reduce the fractured forearm. During the next nine years he had no further trouble. At the age of 14, a lump on the left wrist was first noted, together with some weakness as compared with the right. Later he noted that the left arm was shorter than the right. The weakness persisted, but did not handicap him in his typewriting. Figure 6 shows the marked shortening of the left forearm as compared with the right.

CONCLUSIONS

1. Even after adequate reduction of an epiphyseal fracture a premature ossification with a resultant wrist deformity may ensue.
2. A follow-up of these fractures should extend over a period of at least two years.
3. Conjugal chondrectomy should be done as soon as a definite diagnosis of premature ossification can be made; this requires careful observation and frequent roentgenograms of both forearms.
4. The amount of longitudinal growth to be expected from the upper epiphysis of the radius is small, so the ulna should be excised at the level of the articulating surface of the radius.
5. Conjugal chondrectomy is a simple procedure and gives a well functioning wrist. If done early enough it would probably prevent muscle weakness and atrophy.

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INCIDENCE OF NODULES IN THE THYROID

A COMPARATIVE STUDY OF SYMPTOMLESS THYROID GLANDS REMOVED AT AUTOPSY AND HYPERFUNCTIONING GOITERS OPERATIVELY REMOVED *

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MINNEAPOLIS

The presence of nodules within an otherwise normal thyroid gland is well recognized. Whether or not these nodules have any definite significance has long been a debated question. It has been thought that they represent developmental processes that occur in the natural course of development and indicate no significant feature. They have also been considered as involutinal bodies, representative of the stages in hyperthyroid diseases, and they have been looked on as true tumors arising from germinal centers and having the significance of benign neoplasms. Whichever may be the case, their definite significance has never been proved.

If one is to establish the normal for a given district by assuming that the majority represents the normal, then one must accept the presence of nodules in the thyroid gland as a normal characteristic in Minnesota. It is, however, more probable that these nodules represent an attempt to establish a physiologically normal gland, and to that extent they may be considered physiologically normal.

The presence of nodules in goitrous thyroid glands has likewise been a controversial point. Any proof to indicate their etiologic significance has not been definitely established.

A comparative study of the incidence of nodules in a postmortem series without symptoms referable to the thyroid gland and in hyperfunctioning goiters removed at operation would be of interest and may be able to throw some light on the reason for their existence. With that point in view, this study has been undertaken. The operative specimens constitute the group of cases classified as exophthalmic goiter and hyperfunctioning adenomatous goiter. The postmortem series is composed of supposedly normal thyroid glands removed from unselected patients dying of diseases other than those of the thyroid gland.

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REVIEW OF THE LITERATURE

Goiter is found in all parts of the world, but its incidence may vary greatly in different localities. In Europe the goiter districts are known to comprise southern France, southern Germany, Switzerland, southern Austria and northern Italy. Within these goitrous districts the incidence is likewise exceedingly variable. Steiner,¹ in reviewing the goiter situation in Switzerland, demonstrated that the incidence of goiter in different cantons may vary from 5.7 per cent to 80.4 per cent. In Spain, Maranon² pointed out that all the mountainous districts exhibit goiter, often representing an incidence as high as 25 per cent. In Asia practically all of the Himalaya districts are in a goitrous belt, the incidence being as high as 20 per cent in some localities. Hirsch³ pointed out the presence of goiter in the region of the Andes Mountains in South America and in Central America.

In the United States goiter is found endemic in the northern states, most frequently in the Pacific Northwest and in the regions of the Great Lakes. This geographic distribution is illustrated by Carter⁴ in his material collected from the draft board statistics. From these figures it is found that 80.4 per cent of the drafted men presented thyroid enlargement. These figures are confronted with numerous possibilities for error and would be worthless if taken individually to represent the incidence of goiter in any particular locality. But collectively, they indicate the general trend of the distribution of thyroid enlargement. Olesen and Clark⁵ studied the incidence in Minnesota and found that of 4,061 students examined between the ages of 5 and 23 years, 40 per cent of the boys and 71 per cent of the girls had enlargement of the thyroid gland.

The parallelism between the diffuse goiter and nodular goiter is very evident in some localities; whereas in others it is quite divergent, as Steiner⁶ has shown in Switzerland. In one canton where goiter was

1. Steiner, Otto: *Der Kropf bei den Stellungspflichtigen der Jahre 1924 und 1925*, Schweiz. med. Wchnschr. **58**:401, 1928.

2. Maranon, G.: *The Present Status of the Problem of Endemic Goiter in Spain*, in *International Conference on Goiter*, New York, Paul B. Hoeber, Inc., 1927, p. 361.

3. Hirsch, August: *Handbook of Geographical and Histological Pathology*, Stuttgart, Ferdinand Enke, 1885, vol. 2, p. 121.

4. Carter, Ezra, G.: *Simple Goiter*: Thesis for the degree of Doctor of Philosophy, Univ. Michigan, 1925.

5. Olesen, R., and Clark, T.: *Thyroid Enlargement Among Minnesota School Children*, Pub. Health Rep. **39**:2561 (Oct. 10) 1924.

6. Steiner, Otto: *On the Diffusion of Endemic Goiter in Switzerland*, in *International Conference on Goiter*, New York, Paul B. Hoeber, Inc., 1927, p. 393.

found in 41 per cent of the inhabitants, he found that 31 per cent were nodular goiters, whereas in another canton where 51.1 per cent of the inhabitants had goiter, only 3.3 per cent contained nodules.

Aschoff⁷ pointed out that nodules are found in thyroid glands in northern Germany, a nongoitrous district, just as frequently as they are in southern Germany, but that those in the goitrous districts are much larger. He suggested that the nodule is a sort of tumor rest that exists in every human thyroid gland, but that these tumor rests show intensive growth only under favorable stimulation, whatever that stimulation may be.

ADENOMAS IN THE THYROID GLAND

The adenomas have been generally classified into two main groups, the colloid adenoma and the fetal adenoma. The consensus as to what constitutes a colloid adenoma is well established; namely, that it is a localized area with proliferative or involutional changes of the follicle with large colloid-containing acini, usually encapsulated. The histologic structure may be in all respects similar to that of the normal parenchyma, except that there is no separation into lobules by fibrous tissue stroma, as is seen in the normal thyroid gland.

Fetal adenomas are those in which the structure resembles that seen in the fetal thyroid gland. Wegelin⁸ referred to them as parenchymatous nodules, and classified them into three types according to their structure, calling them trabecular, tubular and small follicular adenomas. He, however, considered them all fundamentally the same.

Intermediate nodules are those exhibiting characteristics of each of the other two types within its structure, as described by Bell.⁹

Degenerate nodules constitute all those in which degenerative changes have occurred, as cystic, fibrous, hyaline, calcareous, hemorrhagic, etc. Originally these may have been any one of the other types of nodules that had undergone degenerative changes. Woelz,¹⁰ in making a comparative study of the various types of goiter in Basel and Berne, observed that degenerative changes were found more frequently in the goiters of Basel than in those of Berne. She believed that this could

7. Aschoff, Ludwig: *Pathologic Anatomy of Endemic Struma*, in *International Conference on Goiter*. New York, Paul B. Hoeber, Inc., 1927; *The Goiter Problem, Especially the Goiter of Puberty*, in *Lectures on Pathology*, New York, Paul B. Hoeber, Inc., 1925.

8. Wegelin, C.: *Die Schilddrüse*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8.

9. Bell, E. T.: *Textbook of Pathology*, Philadelphia, Lea & Febiger, 1930.

10. Woelz, Emilie: *Vergleichende Untersuchungen über die Häufigkeit der verschiedenen Kropfformen in Basel und in Berne*, *Schweiz. med. Wchnschr.* **51**:625, 1921.

be explained by the fact that colloid nodules are more prone to develop degenerative changes than the fetal type of nodule. The latter are found more frequently in the goitrous district of Berne, whereas colloid nodules are found more frequently in Basel, which lies toward the periphery of the region endemic for goiter.

There are two prevailing opinions with regard to the formation of adenomas. That formulated by Wölfler¹¹ and Ribbert¹² postulates that adenomas of the thyroid arise from embryonal cell rests scattered throughout the thyroid tissue. Wölfler has classified these types of adenoma as fetal because of their similarity in structure to that of the thyroid in the fetus. His conclusions were based on operative material of fully developed goiters, deducing from their histologic structure his conclusions that the nodules arose from embryonal cell rests. Hitzig¹³ and Michaud,¹⁴ investigating the structure of adenomatous goiters and examining many from young persons, came to the conclusion that the nodules were not embryonal rests, but that they developed from normal thyroid tissue by metaplasia of the epithelial cells within a localized area replacing the normal tissue, thereby forming a complete secondary lobule or nodule. More recently Kramer,¹⁵ Vogel,¹⁶ Hueck,¹⁷ Kline¹⁸ and others have expressed the same opinion.

Aschoff is of the opinion that nodules develop as tumors and not as localized hypertrophy and hyperplasia. Kramer observed that the epithelial proliferation that leads to the formation of adenomas has its origin in the centrally situated follicles of the thyroid lobule. Aschoff called these centrally situated follicles canaliculi, and expressed the belief that they are rests of germ material from which the other follicles

11. Wölfler, Anton: Ueber die Entwicklung und den Bau des Kropfes, *Arch. f. klin. Chir.* **29**:1, 1883.

12. Ribbert, Hugo: Das Adenom der Schilddrüse, Frankfurt. *Ztschr. f. Path.* **18**:55, 1916.

13. Hitzig, Theodor: Beiträge zur Histologie und Histogenese der Struma, *Arch. f. klin. Chir.* **47**:464, 1894.

14. Michaud, Louis: Die Histogenese der Struma nodosa, *Virchows Arch. f. path. Anat.* **186**:422, 1906.

15. Kramer, L.: Ueber die Rückbildungsvorgänge in den Schilddrüsen Adenomen, Inaug. Diss., Frieberg, 1910, quoted by Wegelin, C.: Die Schilddrüse, in *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8.

16. Vogel, Herbert: Beiträge zur pathologischen Histologie der Schilddrüse, *Virchows Arch. f. path. Anat.* **217**:204, 1914.

17. Hueck, Herman: Ein Beitrag zur Beurteilung der Knoten in der Schilddrüse, *Deutsche Ztschr. f. Chir.* **174**:185, 1922; Zur Frage des Parallelismus zwischen klinischen und histologischen Bild der Struma, *Arch. f. klin. Chir.* **130**:178, 1924.

18. Kline, B. S.: The Origin of Adenomatous Goiter, *Am. J. Path.* **1**:235, 1925.

of the thyroid have developed. Bürkle de la Camp¹⁹ was of the same opinion. In referring to the development of colloid nodules, Rienhoff²⁰ spoke of involutional bodies, and he believes that these areas represent a stage in the disease of hyperthyroidism. Hertzler²¹ referred to them as bosselated areas on a similar basis.

Graham²² expressed the belief that the development of nodules can be explained by a single process rather than by multiple processes or mechanisms of fundamentally different character. He believes that there is a difference in degree of reversion, growth, differentiation and encapsulation which produces the various gross and microscopic pictures that may be observed in nodular goiter. He considered nodular goiter related to the hyperplastic phases of thyroid overgrowth, and that the process of nodular formation may have its inception at any stage in the life of the individual. Wangensteen²³ observed that the blood supply in the region of an adenoma or in the region of degenerating areas is usually poor. This may also be a factor in the development of adenomas.

INCIDENCE OF NODULES

Nodules occur infrequently in the thyroid glands of young persons, but Wegelin⁸ found 1.9 per cent in those of children under 10 years of age. The thyroid glands of more than half of the persons in Berne over 20 years of age have nodules, and in persons over 60 years of age it is uncommon to find glands without nodules. Wegelin found 73.3 per cent in men and 88.4 per cent in women over 25 years of age. Jaffé²⁴ found in the region of Chicago that nodules occurred in 30 per cent of men and 44.7 per cent of women over 20 years of age. He

19. Bürkle de la Camp: Einteilung der strömosen Erkrankungen des Schilddrüse von pathologisch anatomischen Gesichtspunkten aus unter Berücksichtigung ihrer klinischen Erscheinungen, *Arch. f. klin. Chir.* **130**:207, 1927.

20. Reinhoff, W. F., Jr.: Thyroid Gland, in Lewis, Dean: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, 1928, vol. 6, chap. 1; Gross and Microscopic Structure in Thyroid Gland in Man, *Arch. Surg.* **19**:986 (Dec.) 1929; Histologic Changes Brought About in Case of Exophthalmic Goiter by Administration of Iodine, *Bull. Johns Hopkins Hosp.* **37**:285, 1925. Reinhoff, W. F., and Lewis, D.: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, *Arch. Surg.* **16**:79 (Jan.) 1928.

21. Hertzler, A. E.: *Diseases of the Thyroid Gland*, St. Louis, C. V. Mosby Company, 1929.

22. Graham, A.: Nodular Goiters; Their Relation to Neoplasia, *Am. J. Surg.* **7**:163, 1929.

23. Wangensteen, Owen H.: The Blood Supply of the Thyroid Gland with Special Reference to the Vascular System of the Cretin Goiter, *Surg., Gynec. & Obst.* **48**:613, 1929.

24. Jaffé, R. H.: The Variation in Weight of the Thyroid Gland and the Frequency of Its Abnormal Enlargement in the Region of Chicago, *Arch. Path.* **10**:887 (Dec.) 1930.

referred to the fact that there is a constant increase in the frequency of nodules with advancing age. The work of Klöppel, Davidsohn,²⁵ Clerc²⁶ and Hueck²⁷ would also indicate that the incidence of nodules increases with advancing age. Hellwig²⁷ made a comparison between goiters from North America and goiters from Switzerland, and he came to the conclusion that there is a definite difference between them, particularly in the percentage of the various types of goiter. Basing his work on operatively removed specimens, he found that 47 per cent of the goiters from Kansas contained nodules, whereas in his cases studied in Freiburg, the incidence of nodules was 77 per cent, and in Rostock it was 32 per cent.

Woelz,¹⁰ in calculating the relative frequency of the various types of goiter occurring in Switzerland, as based on the histologic examination of operatively removed specimens from Basel and Berne, showed that 92 per cent of the cases were nodular.

METHOD OF COLLECTING AND PREPARING MATERIAL

The material used was collected at the University of Minnesota from the Minneapolis General, the Ancker and the University hospitals between January, 1929, and January, 1931. It represents 390 glands removed post mortem and 165 glands removed at operation. The cases were collected from corresponding age groups and from corresponding localities, and represent a fair distribution for the state of Minnesota.

The postmortem series includes the glands of persons dying of numerous causes. No attempt was made to select the patients, except to exclude those who presented a definite history of hyperfunctioning thyroid disease or in whom there was a very evident goiter on casual inspection post mortem. Large glands that were not observed before removal of the gland were not excluded from the series. All of the operatively removed glands were taken from patients on whom thyroidectomy was performed for hyperfunctioning thyroid disease. This included exophthalmic goiter and adenomatous goiter with hyperthyroidism. The ages of the persons from whom the thyroid glands were obtained ranged between 11 and 75 years. This distribution is indicated in table 1. A definite prevalence of males can be observed in the postmortem series, whereas a definite prevalence of females can be observed in the postoperative series.

All glands were cut into sections 3 mm. thick and examined grossly. The number of nodules were counted in each gland and their size measured in millimeters. Where more than one nodule was found in each gland, the average size was tabulated. The type of nodule was determined by gross and microscopic

25. Davidsohn, Carl: *Der Bau der Kröpfe und seine Bedeutung für Function und Krankheit*, Berl. klin. Wchnschr. **48**:2070, 1911; *Ueber den Schlesischen Kropf*, Virchows Arch. f. path. Anat. **205**:170, 1911.

26. Clerc, Edward: *Die Schilddrüse in hohen Alter, von 50 Lebensjahr an aus der norddeutschen Ebene und Küstengegend sowie aus Berne, Frankfurt*. Ztschr. f. Path. **10**:1, 1922.

27. Hellwig, C. Alex.: *Morphological Changes in Exophthalmic Goiter Following the Use of Lugol's Solution*, Surg., Gynec. & Obst. **27**:173, 1928; *Form und Funktion des nordamerikanischen Kropfes*, Arch. f. klin. Chir. **154**:1, 1929.

examinations. Because of the great discrepancy in the number of cases in the male between the two series, only the female glands were used in these calculations. It is assumed that if satisfactory comparisons could be made of the male glands, similar results would be observed.

THE WEIGHT OF THE THYROID GLANDS

The average weight of the thyroid glands in the postmortem series was less than that in the postoperative series. The average weight of glands with nodules, post mortem, was 42.02 Gm., and postoperatively was 99.55 Gm. The average weight without nodules, post mortem, was 25.99 Gm., and postoperatively was 61.79 Gm.

It is to be remembered, however, that in the postoperative series, from one fourth to one half of a normal-sized lobe was allowed to

TABLE 1.—*Distribution According to Age in the Postmortem and Postoperative Series*

Ages	Postmortem Series Number of Cases		Postoperative Series Number of Cases	
	Female	Male	Female	Male
11-15.....	7	1	1	0
16-20.....	13	7	3	3
21-25.....	10	8	18	2
26-30.....	10	12	13	2
31-35.....	10	11	18	0
36-40.....	19	15	21	5
41-45.....	16	15	20	3
46-50.....	14	21	18	6
51-55.....	12	30	12	0
56-60.....	14	25	6	3
61-65.....	13	31	2	1
66-70.....	10	39	6	0
71-75.....	3	24	2	0
Total.....	151	239	140	25

remain, and therefore these weights give only an indication of the definite increase in size of the thyroid gland in goiters and do not represent the actual weight of the goitrous thyroid glands.

A wide range of variability was observed in both series of cases, but the postmortem series appeared to lie within a definite limit of from 10 to 65 Gm., whereas the postoperative series ranged from 10 to 300 Gm. or more. The glands containing nodules had a wider range of variability in weight than those without nodules.

NODULES

Incidence of Nodules.—The incidence of nodules in the postoperative series was 57.14 per cent, and in the postmortem, 56.95 per cent. As the individual becomes older, the incidence of nodules becomes greater. This increase in the incidence with advancing age was observed in both series, so that in persons between 70 and 75 years of age 100 per cent

of the glands are found to contain nodules. A comparison of the incidence of nodules as found by Klose ²⁸ and Hellwig with this series will be of interest.

Number of Nodules per Gland.—The number of nodules per gland was variable in the two series, the significance of which cannot be definitely established. Their incidence is observed in table 3, as well as a comparison of these results with Hellwig's incidence for Kansas.

The discrepancy of the figures in the two series indicating fewer multiple nodules in the operatively removed glands than in the glands removed post mortem may be due to the fact that nodules were occasionally allowed to remain in the portion of the gland that was not removed, as would occur in simple enucleation of one nodule or in the

TABLE 2.—Incidence of Nodules in the Material of Three Investigations

	Klose		Hellwig		Present Series	
	Frankfort, per Cent	Frelburg, per Cent	Rostock, per Cent	Kansas, per Cent	Postmortem, per Cent	Postoperative, per Cent
Diffuse.....	56	23	68	53	43.05	42.86
Nodular.....	44	77	32	47	56.95	57.14

TABLE 3.—Incidence of Nodules in Glands Removed Post Mortem and at Operation and Comparison of These Results with Hellwig's Series

	Present Series		Hellwig Postoperative
	Postmortem, per Cent	Postoperative, per Cent	
One nodule per gland.....	26.7	36.7	63.29
More than one but less than twelve.....	37.2	20.26	
More than twelve nodules.....	36.0	43.03	
Multiple nodules	34 (72.4%)

resection of only one lobe. This would seem to indicate, however, that the multiplicity of nodules was not increased as a result of the presence of hyperthyroidism, as has been suggested by Rienhoff.

Size of Nodules.—The size of the nodules in the postoperative series was distinctly larger than in the postmortem series, but they did not appear to have any definite size for any age period, as has been previously demonstrated to occur during the life cycle of the normal thyroid gland.²⁹ Their variability in size was just as marked in the younger ages as in the older ages. In the postmortem series the average size of the nodules was

28. Klose, Heinrich: Die pathologisch anatomischen Grundlagen der Basedow-schen Krankheit, Bruns' Beiträge z. klin. Chir. **102**:1, 1916. Klose, H., and Hellwig, A.: Ueber Bau und Funktion der kindlichen Schilddrüsen-Hyperplasia, Arch. f. klin. Chir. **124**:347, 1923.

29. Rice, C. O.: The Life Cycle of the Thyroid Gland in Minnesota, West. J. Surg. **39**:925 (Dec.) 1931.

seen to increase during puberty, to decrease during early adult life and to increase again after 35 years of age, reaching the maximum at 65 years, after which the nodules decrease slightly to the end of the life span. A similar curve could not be detected in those in the postoperative series. This would be expected, however, for here the normal cycle of the gland has been interrupted by disease.

Types of Nodules.—The percentage of the various types of nodules in the adenomatous glands is stated in table 4, which does not imply that each gland contained only one type of nodule, for very often all types of nodules were found in each gland. If one is to consider the glands that contained only one type of nodule within its structure, the proportions cited in table 5 were observed.

TABLE 4.—Percentage of Types of Nodules in Adenomatous Glands

	Postmortem Series, per Cent	Postoperative Series, per Cent
Colloid.....	82.5	66.25
Fetal.....	25.5	33.75
Mixed.....	6.9	25.00
Degenerate.....	15.1	37.50

TABLE 5.—Percentage of Glands with Only One Type of Nodule

	Present Series				Hellwig Kansas		Woelz				Wydler Berne, %
	Postmortem		Postoperative				Berne		Basel		
	No.	%	No.	%	No.	%	No.	%			
Colloid.....	54	62.79	22	27.5	29	62	14	23.64	261	55.0	9
Fetal.....	8	9.3	10	12.5	12	25	147	46.9	47	9.9	64
Mixed.....	2	2.32	7	8.75
Degenerate.....	3	3.48	6	7.5
Multiple types.....	19	22.09	35	43.75	6	13	92	29.4	166	35.0	27

The significance of this difference in the various types of nodules in the postoperative and postmortem series can only be postulated. It may be that the same factors that produce hypertrophy and hyperplasia also produce an effect on the nodule which changes its structure from that of a colloid nodule to one of the other types, for it is observed that the colloid nodule is decreased in number, whereas the fetal, mixed and degenerate nodules are increased in number in the operative specimens. This would correspond to the idea of Graham, who deduced that other types of nodules are an involutional or degenerative stage of a colloid nodule. He expressed the belief that the development of nodules is dependent on a single process, and that the difference in degree of reversion, growth, differentiation, encapsulation, etc., offers a satisfactory explanation of the gross and microscopic variations observed in nodular goiters. This conception makes it unnecessary to explain the development of nodules on a fetal rest theory.

INCIDENCE OF VARIOUS TYPES OF GOITERS

In dividing the postoperative series into three groups, those showing diffuse hypertrophy without nodules, diffuse hypertrophy with nodules and adenomatous goiters, with hyperthyroidism, the percentages given in table 6 were observed.

It is seen that 65 per cent were exophthalmic goiters. Thirty-three and eighty-four hundredths per cent of these exophthalmic goiters contained nodules within their structure.

Lymphocytic foci were found in 9.8 per cent of the glands examined post mortem and in 67.85 per cent of the glands examined post-operatively. Seventy-nine and twelve one-hundredths per cent of the exophthalmic goiters contained lymphocytic foci, and 46.93 per cent of adenomatous goiters with hyperthyroidism contained lymphocytic foci.

Wilson³⁰ has shown that there is a small but definite difference between adenomatous goiters that presented symptoms of hyperthyroidism and those that were nontoxic. In examining approximately 250 cases of each group, he found that in those which had presented symptoms of

TABLE 6.—Incidence of Various Types of Toxic Goiters

	Per Cent
Diffuse hypertrophy (exophthalmic goiter) without nodules.....	42.85
Diffuse hypertrophy (exophthalmic goiter) with nodules.....	22.14
Adenomatous goiter with hyperthyroidism.....	35.00

hyperthyroidism, 90 per cent showed microscopic evidence of hypertrophy and hyperplasia, and in the nontoxic group, 95 per cent showed no evidence of hypertrophy and hyperplasia. He compared the most marked evidences of hypertrophy and hyperplasia in toxic adenomas with those of exophthalmic goiter of the mildest degree, and concluded that in the toxic group the hyperthyroid symptoms could be due to the proliferative changes and increased secretion of toxic material, whereas in the nontoxic group there is not a sufficient amount of this substance secreted to cause the hyperthyroid symptoms.

CONCLUSION

Nodules occur as frequently in the postmortem thyroid gland that is assumed to be physiologically normal as in hyperfunctioning goiter operatively removed. The greater prevalence of colloid nodules in the postmortem thyroid gland may be due to the fact that differences in the degree of reversion, growth, differentiation and encapsulation have not been forced on the normal gland as strongly as they have in the

30. Wilson, L. B.: The Pathology of Nodular Goiters in Patients With and in Those Without Symptoms of Hyperthyroidism, *Am. J. M. Sc.* **165**:738, 1923.

toxic goiter. Multiple nodules are not found more frequently in hyperfunctioning goiters than they are in physiologically normal thyroid glands. Nodules are found in 56.95 per cent of the physiologically normal thyroid glands and in 57.14 per cent of the toxic goiters. Forty-two and eighty-five hundredths per cent of the toxic goiters have no nodules and are manifested as exophthalmic goiter. Thirty-five per cent of the thyroid glands that become hyperfunctioning can be classified as adenomatous goiter with hyperthyroidism. The remaining 22 per cent of glands contain nodules, but manifest their hyperthyroidism as exophthalmic goiter. Diffuse hyperplastic goiter (exophthalmic goiter) occurs proportionately as frequently in glands with nodules as in glands without nodules. Lymphocytic foci are found more often in hyperfunctioning goiters than in normal thyroid glands. From these observations it appears that the presence of nodules in the thyroid gland is physiologically normal, and that the incidence is not appreciably altered by the development of hyperthyroidism.

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomalies.—Jacobs¹ stated that in horseshoe kidney either the upper or lower poles of both kidneys fuse, the latter condition being more common. The parenchyma of the fused part which lies anterior to the great vessels varies in amount. The ureters, usually two, arise from separate pelves and pass anterior to the isthmus, but because of their unusual position and curvature the kidneys are predisposed to obstruction, infection and stone.

Jacobs reported two cases of horseshoe kidney. In the first case, albuminuria led to a roentgenographic examination and the discovery of calculus. Bilateral pyelographic examination disclosed the lateral position of the ureteropelvic juncture. The isthmus was divided at operation, but a urinary fistula persisted due to cutting across a calyx in the resected portion of the isthmus. In the second case, there was backache and hematuria, with hydronephrosis on the left side and the calices directed mesially. The right kidney was normal. Operation was not performed.

Operation in cases of horseshoe kidney is materially assisted by a previous knowledge of the existence of the condition. Bilateral pyelograms are the best means of making a diagnosis. Abnormalities are due to failure of rotation of the renal pelvis. The axis of the calices is median or anterior, and the ureter leaves laterally or anteriorly.

1. Jacobs, Arthur: Horseshoe Kidney: A Report of Two Cases, Brit. M. J. 2:8 (July 5) 1930.

[ED. NOTE.—In one of these cases a urinary fistula persisted after resection. It is only rarely that a portion of the pelvis or one of the calices extends down into the isthmus. If this area is sutured over, fistula seldom results. There have been few cases reported of fistula occurring after resection. In one case a large pelvic stone extended down into the isthmus. Accurate closure was carried out; there was no urinary leakage.]

As the author stated, the correct diagnosis of renal anomalies, especially of horseshoe kidney, materially affects surgical prognosis. The abnormal structural relations, the unusual attachments and the unrotated position of the renal pelvis require a surgical approach different from that employed in dealing with kidneys normally situated. The numerous and anomalous blood vessels, and the fixity and situation of the renal mass necessitates accurate anatomic recognition of the condition for the carrying out of any successful surgical procedure.]

Collins² summarized the data in 581 cases of congenital unilateral renal agenesis, which were divided about equally between men and women. The kidney was absent on the left side in 318 cases, on the right side in 238, and the side was not stated in 25. The average weight of the remaining kidney in 87 cases was about 280 Gm. (normal, 150 Gm.). The remaining kidney was normal in 281 cases, diseased in 179 and the condition was not stated in 121. In 110 cases death was due to disease of the genito-urinary tract. The condition was diagnosed at necropsy in 439 cases, by clinical and surgical methods in 124 cases and in 18 it was not stated. There were anomalies of the internal genitalia in 338 cases. One ureter was absent in 297 cases, and other ureteral anomalies were observed in 284 cases.

In 65 per cent of cases noted in the literature, congenital absence of one kidney was observed in subjects whose average age was 40 years; 68 per cent of these had died of diseases totally unrelated to the genito-urinary system. In the presence of disease of the genito-urinary system, extensive surgical procedures on the urinary tract cannot be carried out, and the most conservative measures compatible with arresting the disease must be instituted.

Resection.—Campbell³ reported two cases of ureteroheminephrectomy successfully performed on female infants, aged from 6 to 28 months, for ureterohemipyonephrosis. In one case an ectopic ureteral opening was present and at first made the diagnosis difficult. Ectopic ureteral openings, because of urinary leakage, usually result in classify-

2. Collins, D. C.: Congenital Unilateral Renal Agenesis, Proc. Staff Meet. Mayo Clin. 6:581 (Sept. 30) 1931.

3. Campbell, M. F.: Uretero-Heminephrectomy in Infancy, J. Urol. 26:433 (Sept.) 1931.

ing the condition as enuresis. One of these cases is the seventh reported of this type in which ureteral ectopy did not result in urinary incontinence. The treatment of hemipyonephrosis is surgical. Infants withstand radical operation on the urinary tract well. Proper preoperative and postoperative care must be taken, since severe acidosis is likely to develop during the first forty-eight hours following operation.

Smith and McKim⁴ stated that renal resection is possible, and when indicated in selected cases should include the resection of all diseased tissue. The presence of both kidneys is not absolutely necessary. When the pelvis is opened, urinary fistulas may result; with the lumbar approach and improved technic this is uncommon. The resected kidney will attempt to restore its normal rounded contour and free itself from adjacent adhesions. The remaining portion of the renal parenchyma will attempt to maintain its function, although that portion near the area of resection will become sclerosed due to involvement in scar tissue and the possible occlusion of the vascular supply.

Smith and McKim reported 2 cases in which resection was successfully performed. They emphasized the importance of conserving renal parenchyma and the possibility of conservation instead of complete destruction, after a careful analysis of the data obtained on modern urologic examination.

Ptosis.—Kidd⁵ stated that the incidence of movable kidney, as shown by figures taken at random from outpatients at St. Thomas' Hospital by Mackenzie, is 20 among 100 female patients, but only 4 had symptoms; of 515 there were 411 (80 per cent) who did not have symptoms. Of 400 male patients, 4 had movable kidney but only 1 had symptoms. The condition is a disease of adult life.

The support of the kidneys in health is intra-abdominal pressure which is maintained by the tonus of the unstretched muscles of the abdominal wall if persons have well formed chests and the upper part of the abdomen has sufficient cubic space to hold the heart, lungs and supra-umbilical viscera. Adequate support presupposes a well balanced neuromuscular reflex arc. Anchors of the kidneys of healthy persons are the blood vessels in the pedicle of the kidney, the attachments of the peritoneum to the posterior abdominal wall, and the perinephric fibrofatty bands which suspend the kidney from the perinephric fascia. The perinephric fibrofatty acts as a suspensory ligament and as a lubricating mechanism which adapts the moving kidney to its fixed surroundings. If the muscles fail, if the thorax grows too narrow, or if there arises

4. Smith, P. G., and McKim, G. F.: The Resection of Localized Areas of Pyo- or Hydronephrosis in the Congenitally Normal Kidney, *J. Urol.* **25**:203 (Feb.) 1931.

5. Kidd, Frank: Acquired Renal Dystopia or Movable Kidney, *J. Urol.* **26**:327 (Sept.) 1931.

sudden trauma, the restrainers of movement or the ligament of the kidney become stretched and thick, and have to take an increasing share in supporting the kidney. Under such circumstances certain symptoms are likely to arise, and a too movable kidney becomes diseased.

The following types of renal dystopia are classified according to their hypothetic cause: 1. The type due to lax abdominal muscles occurs when these muscles have grown slack, as after pregnancy, after the removal of large abdominal tumors, after cutting at operation of the nerves which supply the abdominal wall, or from lack of exercise or improper breathing with the abdomen instead of the thorax, and in states of asthenia. 2. Compression of the hypochondrium stretches the ligaments of the kidney and may be due to rickets or to tight-lacing. 3. The ectopic or unascended kidney of the congenital type is due to failure of the kidney to ascend into its proper position in the loins during fetal life. 4. The narrow flat thorax and the narrow abdomen, good abdominal muscles and a weak nervous system includes two types, one type in which the thorax is wide but flat and the other in which it is flat, narrow and too long. In both types there is a narrow subcostal angle, without space for the supra-umbilical viscera, so that the liver and right kidney and sometimes the other viscera are pushed down into the abdomen.

Various opinions prevail as to the advisability of operation. In certain instances operation is advocated in all cases of movable kidney, with the belief that cure will be effected not only of the renal symptoms but of the mental symptoms which are alleged to be secondary to it. Other physicans neglect the movable kidney and treat only the weakened nervous system, and still others apply certain principles for selecting cases suitable for operation, with the employment of adequate technic. Cases of severe general splanchnoptosis, tuberculosis, chronic cough, disease of the heart and confirmed congenital neurasthenia are excluded as unsuitable for surgical measures. Cases are selected in which there are intermittent attacks of renal drag relieved by recumbency, superadded attacks of pyelitis, a definite history of sudden onset after severe trauma or congenital ectopic kidney. Six months of palliative treatment is tried in most cases. Pyelography determines the suitability of cases for operation. It shows whether there is a fixed twisting, kinking or S-shaped bend of the upper part of the ureter, as a consequence of which there is dilatation and ballooning of the pelvis of the kidney. The need for operation is further indicated if catheterized urine from the ureter shows that the pelvis of the kidney is infected.

Kidd has devised an operation to insure fixing the kidney in the proper position. The salient points of his technic are as follows: A small incision is made, and the muscles are split whenever possible with conservation of the nerves. The incision begins in the costovertebral

angle and extends directly downward until it strikes the edge of the latissimus dorsi muscle, and then it passes anteriorly parallel to the last rib. The perinephritic fat is cleaned off completely, and the renal vessels and upper end of the ureter are denuded, so as to denervate these structures. The fibrous capsule of the kidney is removed from the upper two thirds of the kidney and rolled down over the lower third. Stitches are then put through the rolled portion of the fibrous capsule and brought out through the posterior abdominal wall up above the external arcuate ligament and through the diaphragm above the twelfth rib. The patient remains flat on the back for ten days, and the foot of the bed is elevated on blocks. When the patient arises from bed, a course of abdominal exercise is prescribed.

Tumors.—Prather and Crabtree⁶ reviewed 111 cases of the mixed embryonic type of renal tumors among children. Approximately 77.5 per cent of the tumors were of the embryonic adenosarcoma group. Other types in the series were round cell sarcoma, spindle cell sarcoma, myxosarcoma, leiomyo-adenosarcoma and rhabdomyo-adenosarcoma. A moderate number of the adenocarcinomas contained cysts or revealed cystic degeneration. Forty-six and one-tenth per cent of the patients were boys, and 53.9 per cent were girls. The average age was 2.7 years. The relative incidence of tumors of the kidney to tumors in general is 20.4 per cent among children, and 0.5 per cent among adults.

A mass is usually the initial symptom; hematuria and pain are less common. In the 111 cases the first symptom was a mass in 80.1 per cent, hematuria in 14.5 per cent and pain in 5.4 per cent.

The treatment of mixed tumors of the kidney of children is early complete excision, although the absence of symptoms often makes this impossible. Surgical removal of the tumors is not particularly difficult, due to the fact that they are still encapsulated. There is a tendency for the growth to adhere to the peritoneum and large intestine, the latter being displaced mesially. Three methods of approach are employed for removal of these kidneys: lumbar extraperitoneal, median line or rectus transperitoneal and lumbar peritoneal. Of the operative procedures described since 1924, 67 per cent were done by the transperitoneal route and 33 per cent by the lumbar extraperitoneal route. The type of incision does not seem to influence the rate of mortality or end-result. Radium and roentgen rays have been used, but not with satisfactory results.

Wheeler estimated that 80 per cent of tumors of the kidney recur within a year. Warner estimated that the immediate and remote mortality is from 70 to 90 per cent. In the series of 111 cases, 12.3 per

6. Prather, G. C., and Crabtree, E. G.: Kidney Tumors in Children, *J. Urol.* 25:589 (June) 1931.

cent of the patients lived two years or longer following operation, 18.4 per cent died within a month of operation and 69.3 per cent of those who survived operation for one month or those who were not operated on, were dead in fifteen months. Although the general outlook in these cases is not favorable, the cures from operation are sufficient to encourage the procedure in the cases in which the growth is not unduly large and is not broken through the capsule.

[ED. NOTE.—The outlook for cure of children with mixed embryonic tumors of the kidney remains relatively poor. Early diagnosis constitutes one of the most difficult phases of the situation. If the tumor could be removed at the beginning of its clinical course, the chance of cure would be fair. It is the uniform opinion that radiotherapy has little to offer in this field.]

The frequency of renal tumors during childhood as compared with neoplasms in general during this period is noteworthy and could well be emphasized in campaigns for education concerning carcinoma. The advantage of frequent health examinations of children might be stressed, and renal tumor could be included in the lesions to be looked for by the examining physician.]

Sanford⁷ reported a case of carcinoma of both kidneys. Right nephrectomy was done as the only possible means of prolonging life. The upper pole was covered with new growth. A section showed that the kidney was invaded with groups of tumor cells which were arranged in cordlike and alveolar formation. In certain areas the cells were somewhat transitional, as though they had originated from the pelvic mucosa. A diagnosis was made of transitional cell carcinoma of the kidney originating from the pelvis. Three weeks after operation the patient died of uremia. At necropsy, the left kidney was found to be larger than the one removed at operation, and its upper and middle thirds were entirely replaced by a closely packed carcinomatous mass, the gross appearance of which was different from the scattered nodules of tumor in the other kidney.

Orr found that in 7,207 necropsies made in a period of thirty-six years there were 1,046 cases of malignant disease among which were 8 of multiple malignant tumors. In a period of thirty-five years, Jungmanns found that in 36,408 necropsies there were 4,192 cases of carcinoma, of which 19 were multiple; 11 patients were men and 8 were women. In none of these cases were both kidneys carcinomatous.

Bilateral primary malignant renal tumors include sarcoma, nephroma and carcinoma. Statistics of their relative frequency vary widely and are confusing. Paul stated that bilateral primary malignant renal tumors are more common among children than among adults, and that

7. Sanford, H. L.: Carcinoma of Both Kidneys, Surg., Gynec. & Obst. **53**:360 (Sept.) 1931.

50 per cent among children are bilateral. Jacobi found 8 cases of bilateral tumor among 41 renal sarcomas. Kuester reported that of 607 malignant renal tumors, 13 were primary bilateral growths. Nicolich reviewed from the literature 19 cases of apparently primary bilateral malignant renal tumors, in 18 of which sarcoma was present on one or both sides. There was no instance of bilateral carcinoma. Kapsammer, in 69 cases of renal tumors, found 3 primary bilateral tumors.

Morelli⁸ reported on a histologic study of 6 clear cell renal tumors. Two of these tumors were composed of clear cells arranged in cords, greatly resembling the suprarenal cortex; these were classified as hypernephromas. Three were composed of clear and opaque cells in tubular and papillary formation, and were designated clear cell adenocarcinomas. One tumor was mixed adenocarcinoma and hypernephroma. Morelli reserves the term "hypernephroid" for tumors the histogenesis of which cannot be determined.

Hydronephrosis.—Fister and Smith⁹ reported 2 cases of hydronephrosis associated with aberrant vessels, and noted that the first symptom of the condition may appear in infancy. The onset of symptoms of hydronephrosis associated with accessory renal vessels is usually during early adult life.

Opinions vary as to the part these vessels play in the production of hydronephrosis. There are three definite methods by which it may be possible for abnormal vessels to cause urinary stasis leading to dilatation of the renal pelvis: 1. They may act as a mechanical obstruction in the presence of movable kidney or of infection of the kidney and pelvis. 2. They may cause the formation of extra-ureteral adhesions, and in some cases there may be actual ureteral stricture at point of contact. Repeated reinfection of the pelvis of the kidney unquestionably produces periureteritis at the point of crossing of the aberrant vessels, resulting in adhesions and fixation of the ureter. The periureteral adhesions cause narrowing of the ureter which produces urinary retention and hydronephrosis. Continued infection and ureteral irritation eventually will cause actual stricture due to proliferation of connective tissue. 3. According to Quinby, the presence of an anomalous vessel in contact with the ureter is sufficient to cause inhibition of ureteral peristalsis.

The following are some of the symptoms that might suggest the presence of aberrant renal vessels: repeated attacks of pyelitis; absence of calculi; normal urination; normal catheterization of the ureters; intermittent attacks of renal colic; pyelographic evidence of dilatation

8. Morelli, M.: Contributo allo studio dei tumori renali denominati ipernephroidi, Arch. ital. di urol. 7:303, 1931; abstr., Am. J. Cancer 15:3024 (Oct.) 1931.

9. Fister, G. M., and Smith, E. H.: Aberrant Renal Vessels in Children, J. Urol. 26:175 (Aug.) 1931.

of the pelvis of the kidney with a ureteral kink, or narrowing of the upper part of the ureter; a v-shaped retraction of the ureteral orifice, as seen through the cystoscope. A palpable soft tumor is demonstrable in most cases.

Surgical measures are indicated in most cases of hydronephrosis associated with anomalous vessels. Conservative treatment does not afford much relief in advanced cases, and operation in the early cases might often save the kidney. Conservative surgical treatment which removes the obstruction and reestablishes free drainage of urine usually is sufficient in the early cases. Division of vessels, band or adhesions, transplantation of the ureter away from the vessels, nephropexy or plastic operation on the ureteropelvic juncture will relieve the symptoms in some cases. Primary nephrectomy is necessary if much of the kidney is destroyed, and if a serious infection or calculi are present.

[ED. NOTE.—The fact that aberrant renal vessels may produce symptoms in childhood has not been sufficiently appreciated. The clinical picture in this article is excellent. It is generally agreed that noncalculous obstructions at the ureteropelvic juncture should be explored surgically, if conservative treatment by cystoscopic methods does not afford prompt and prolonged relief. Many such obstructive lesions will be found associated with anomalous or aberrant vessels. Division of the vessels and proper attention to drainage of the pelvis into the ureter by pelvioplastic operation, renal fixation, or both, are procedures which, if undertaken early, will save many kidneys that otherwise would become destroyed within a few years.]

Stones.—Herbst¹⁰ stated that recurrence of renal stone after conservative operation for its removal occurs in more than 15 per cent of cases. True recurrence is a new formation of stone after its complete removal. False recurrence is the persistence of stones missed or omitted at the time of operation.

Concentration of the urine is an important factor in the development of urinary lithiasis, since it is more commonly found among persons living in dry, hot zones. In certain areas where the temperature varies from 100 to 130 F., urination is uncommon, since most of the water is eliminated by the skin; the incidence of stone among the natives of this region is almost 100 per cent. Operative trauma, formation of cavity and disturbed drainage with infection are the most significant factors in recurrent renal calculi.

Any disturbance of the renal parenchyma in the removal of stone favors recurrence. Pyelotomy, when surgically possible, is a better surgical procedure than nephrotomy. Cleansing of the pelvis and calices following the removal of stones is important, as sand, small

10. Herbst, R. H.: Recurrent Renal Calculus: Its Cause and Prevention, *Am. J. Surg.* 12:58 (April) 1931.

particles of stone, fragments of tissue and blood clots which are not washed away are possible sources of recurrence. All cavities in the kidney should be lavaged with a solution of sodium chloride before the operation is completed. Incrustations should be removed, and if ulcerations are present, they should be curetted. The drainage from a stone-bearing kidney following operation must be adequate. Narrowing at the ureteropelvic juncture is a common factor in the causation of stone, and should be corrected at operation by thorough dilatation or possibly by plastic operation. It should be dilated subsequently if narrowing recurs.

Because of the part infection plays in the production of stone, an attempt should be made to remove all possible foci of infection before any operation on the kidney is undertaken. The infected cavity should be resected if surgically possible. In cases of severe pyonephrosis due to calculi, preoperative drainage and lavage by means of the indwelling ureteral catheter may be means of cleansing an infected organ and of reducing the operative danger and the possibility of recurrence. In any preoperative roentgenologic study, stones are likely to be overlooked because they fail to produce a shadow on a film taken with the kidney in the body, or stones may be superimposed on one another, producing one shadow. In removing a stone, especially with instruments, a small piece or pieces may be broken off and left behind; these promptly cause recurrence. They may be seen on the film but not at operation. Practically all of these conditions may be avoided by fluoroscopy of the exposed kidney before its replacement.

Von Lichtenberg¹¹ stated that, in rooms in which he performs operations for renal lithiasis, the walls and shades are dark, thus favoring the discovery of stones which may have been left. In the last two years the film method of control has been used to ascertain the situation of stones. A special forceps, shaped like the kidney, is used to draw out the kidney. This instrument has an addition which shows up readily on the plate, and in that way facilitates the recognition of the stone. Although the cassettes and forceps may be boiled, the author believes that the asepsis of the operation may be disturbed.

Stones in the lower part of the ureter are removed by operating in at least 30 per cent of his cases. Early surgical intervention is preferable in a certain percentage of cases.

Newcomb and Ranganathan¹² analyzed 226 urinary calculi. Seventy-three of these were so small that microscopic methods were necessary.

11. von Lichtenberg, Alexander, in discussion on Kidney and Ureteral Stones, *J. Urol.* **25**:181 (Feb.) 1931.

12. Newcomb, Clive; and Ranganathan, S.: The Composition of Urinary Calculi, *Indian J. M. Research* **17**:1037 (April) 1930: abstr., *Ztschr. f. urol. Chir.* **31**:60 (Dec. 18) 1930.

All but 5 of the stones were from the bladder. The average composition was 24.9 per cent calcium oxalate; 7.4 per cent calcium phosphate; 6.9 per cent magnesium ammonium phosphate; 6.2 per cent protein; 49.7 per cent uric acid, and 4.9 per cent various other salts. The latter consist chiefly of carbonates and insoluble ash, and sulphur was found in traces in some stones. Only 26 (11.8 per cent) were pure or uniform stones. The remainder were mixed; the most common combination was urates and oxalates. Urates were found in 187 stones (84.6 per cent), and in 120 cases phosphates were found. The vesical stones were the most mixed in composition, the majority containing a combination of urates or uric acid with oxalates. Of the pure stones, uric acid stones were most frequently found (6.8 per cent). Urates were found in 53 per cent of the stones, oxalates in 17 per cent and phosphates in 12 per cent.

The small number of renal stones, 5, is indicative that such cases are not common in India; the converse is true in America and Europe.

Price and Jacobs¹³ recorded a case of primary squamous carcinoma in a hydronephrotic kidney with renal stones.

The patient, a laborer, aged 54 years, complained of pain in the lumbar region. A large mass could be felt in the left side of the abdomen, extending from under the left costal margin down to the iliac region. The urine contained albumin, blood and pus. Roentgenograms disclosed shadows of at least 11 calculi of varying dimensions in an area extending from below the iliac crest upward to the level of the second lumbar vertebra. At operation, the kidney was exposed through a curved lumbar extraperitoneal incision. The organ was large and extremely difficult to deliver, but this was successfully accomplished after resection of the twelfth rib. Following division of the ureter and ligation of the pedicle, the kidney was removed without further trouble.

The removed kidney measured about 18 cm. from pole to pole and about 11 cm. in its greatest transverse diameter. The surface of the organ was coarsely lobulated, and it was obviously cystic and contained fluid. On hemisection the parenchyma was found to be practically obliterated, being reduced to a thin shell of tissue not more than 1 mm. thick. In the interior of the organ were large cystic spaces, separated from each other by attenuated renal substance and containing fluid. The region normally occupied by the pyramids contained a quantity of dense, partly embedded fibrofatty tissue, in which were a number of large irregular calculi. At the lower pole the dilated calix was partly occupied by a cauliflower-like tumor about 5 cm. in diameter. In the center of the tumor were two irregular spaces occupied by a number of small faceted calculi. Distributed irregularly in the fibrofatty tissue of

13. Price, L. W., and Jacobs, Arthur: Renal Calculi with Squamous Carcinoma in a Hydronephrotic Kidney, *Brit. J. Surg.* 28:590 (April) 1931.

the central portions of the organ, but occupying chiefly the lower half, were several large calculi. Sections of tissue from the tumor occupying the lower pole of the kidney showed the structure of a squamous cell carcinoma. This probably arose in the epithelium of the lower calix, which had undergone squamous metaplasia, as the transitional epithelium in this region showed hyperplasia and in places a definite tendency to assume squamous characteristics.

[ED. NOTE.—There are two types of squamous cell tumors arising in the renal pelvis; in the first type the parenchyma is invaded early, the kidney is solid and compact, and the parenchymal tissue becomes completely replaced by carcinoma and irregular masses of fibrosis; in the second type the growth is confined to the pelvis, the kidney is extremely large and hydronephrotic with pressure atrophy of most of the renal tissue. It is possible that in certain cases the development of the carcinoma of the pelvis may precede the formation of stones. Hallé maintained that the metaplasia does not result from irritation of the stone, but that epidermization and calculi both result from the same chronic inflammation. The stones in the pelvis may be extremely large, and of the staghorn earthy-phosphate type. These tumors are comparatively symptomless. When obstruction occurs, it is from gradual slow occlusion and is almost painless. In contrast to papillary tumors, the squamous cell carcinoma rarely bleeds. The mortality after operation, usually nephrectomy, is high, as the patients die shortly after the operation from local recurrences or metastatic growths.]

URETER

Stricture.—Campbell¹⁴ reported 15 cases of congenital bilateral stricture at the ureterovesical juncture. The patients were infants and children; the condition of 11 was discovered at urologic examination, and of 4 at necropsy. The ages of the 11 patients varied from 2 months to 11 years, and of the other 4 from stillbirth to 6 months.

Sclerosis, increase in localized connective tissue, scarring and inflammation, or only narrowing of the lumen of the ureter without fibrosis may be found. The late results of urinary backpressure with infection are found in the elongated, angulated, tortuous, atonic scarred ureters and in the thinned sclerosed and infiltrated renal tissue. The symptoms are due to infection and to loss of renal function, pyuria being the outstanding objective symptom. Patients usually are treated for chronic pyelitis because of persistent pyuria. In Campbell's cases, the colon bacillus was the predominant invading organism. Gastro-intestinal

14. Campbell, M. F.: Congenital Bilateral Uretero-Vesical Junction Stricture in Infants and Children, *J. Urol.* **26**:529 (Oct.) 1931.

upsets, fever of low grade, anemia, malaise, loss of weight or failure to gain weight are common symptoms. Pain is rare, and if present usually is localized to the loin and is due to hydronephrotic distention. Inflammation of the secondary vesical outlet causes frequency of urination, burning, dysuria or hematuria. Persistent pyuria is the usual indication for complete urologic examination; it was the only cause for investigation in Campbell's cases.

Two characteristic observations may be made: (1) It may be impossible to insert a catheter into the ureter; sometimes not until the second or third examination can even a number 4 French filiform tip be passed; on withdrawing the catheter it is so firmly grasped by the stricture that the wall of the bladder may be pulled with it, and (2) the pyelogram shows a dilated ureter beginning in the region of the stricture and terminating in a hydronephrotic renal pelvis. Following retrograde pyelography, the catheter should be left in position until the injected material has been withdrawn. In this series of cases the combination of catheter grasping, hydronephrotic drip and widely dilated upper tract was found, making the diagnosis of stricture unquestionable.

The object of treatment is to eliminate the obstruction. In 6 of the cases dilation by catheter was carried out. It is usually difficult to pass even a number 4 French catheter at first; after this has been done, two, three or four catheters of the same size may be passed side by side. This technic is required by the small urethral caliber. The procedure is done every ten days at first; then dilation may be done once a month or once in three months according to the rate and degree of recontraction. If satisfactory dilatation is not obtained by cystoscopic methods, transvesical ureteral meatotomy and section of the stricture may be done. Catheters are passed up the ureters as guides. Through the open bladder the stricture is divided against the inlying catheter and cut through to it. Beginning at the ureteral meatus the incision is made upward from 1 to 1.5 cm. Cutting the dense tissues gives the sensation of cutting cartilage. The incised stricture is then widely dilated with a number 14, 16 or 18 French sound, and a whistle tip of soft rubber catheter is inserted from 8 to 12 cm. in the ureter, where it is anchored for a week. These catheters, one from each side, are brought out through the open bladder, and the drainage material is collected. If the patient is extremely ill, with low renal function, preliminary drainage with bilateral ureterostomy is indicated.

Although operative treatment may not always afford complete cure, it offers more than any other method. Medical treatment alone is not adequate. Continued backpressure, renal destruction and uremia produce a fatal outcome.

Hurst and Gaymer-Jones¹⁵ stated that the pathogenesis of enormous dilatation of the ureters without evidence of obstruction has been a controversial subject. It has been attributed to congenital muscular insufficiency, inflammatory atony or to neuromuscular dysfunction. They reported a case of a woman, aged 33, with left megalo-ureter without stenosis of the lower part of the ureter, and advanced the hypothesis that these dilatations are caused by an absence of relaxation of the ureterovesical sphincter. The mechanism of dilatation is compared to that which obtains in cardiospasm and megacolon. It was formerly supposed that the esophageal dilatation and hypertrophy in the former condition was caused by spasm at the juncture of the esophagus and cardia of the stomach, but Hurst observed that it is caused by achalasia or failure of relaxation of the sphincter as the result of disturbance of the intrinsic supply to the nerves. The inert sphincter acts as an obstruction, and excessive propulsive efforts produce hypertrophy and dilatation of the esophagus. The same mechanism applies in cases of megacolon, in which the hypertrophy and dilatation of the colon are caused by achalasia of the anal sphincter of the pelvirectal sphincter.

From the authors' observations, megalo-ureter without evidence of organic obstruction is attributed to degenerative changes in the nerve supply in the pars intramuralis of the ureter. This is the result of inflammation in the mucosa which spreads to the muscularis producing degeneration of nerves which progresses long after the primary inflammation of the mucosa has disappeared. On cystoscopic examination the ureteral orifice is relaxed and patent, and there is no obstruction to the passage of a catheter or "hang" on withdrawal of the bulb.

Moore¹⁶ reported on the clinical and roentgenographic study of approximately 75 cases of ureteral meatotomy performed over a period of seven years, from which he made the following conclusions:

The operation is comparatively minor but technical. The high-frequency meatome, when properly applied, is effectual and safe. It is possible to continue work higher on the ureter at the same sitting without any alarming complications. Stricture does not follow the operation. In a number of cases the ureteral opening was sufficiently large to pass number 7 and 9 catheters, after which there was temporary relief. More permanent relief followed wide incision of the opening. Symptoms or signs of regurgitation were not observed at any time after the operation.

15. Hurst, A. F., and Gaymer-Jones, J.: A Case of Megalo-Ureter Due to Achalasia of the Uretero-Vesical Sphincter, *Brit. J. Urol.* **3**:43 (March) 1931.

16. Moore, N. S.: Ureteral Meatotomy: A Clinical Evaluation, *J. Urol.* **26**: 519 (Oct.) 1931.

Diverticulum.—Bugbee¹⁷ stated that diverticulum of the ureter is rarely seen. It has been produced experimentally. In 4 cases it was found at necropsy, and 7 clinical cases have been reported; to which the author adds 3. Three possibilities as to the etiology of ureteral diverticula are: (1) secondary budding of the metanephric anlage, (2) compensatory structure following congenital stenosis of the ureter and (3) acquired structure occurring late following an acquired ureteral stricture.

In 9 cases of diverticulum of the lower part of the ureter a ureteral catheter was obstructed in its passage, and in all except 2 cases roentgenograms taken afterward showed the catheter coiled in the diverticulum. The diagnosis was verified by a ureterogram in each case. Congenital diverticulum of the ureter may be present and not lead to investigation until later in life when symptoms due to infection or to the formation of calculus arise.

The treatment for diverticulum of the ureter usually is surgical, as in 8 of the 10 reported cases. Two patients were relieved by dilation of the ureter and intra-ureteral manipulation, to establish freer drainage of the diverticulum.

Infection.—Dourmashkin¹⁸ stated that empyema of the ureter does not occur except in the presence of a preexisting diseased state. The local pathologic changes are marked periureteritis, dilatation of the ureter and firm adhesions of the stump to the surrounding tissues. Besides pus, calcified material was found in one of the cases in which operation was performed by Hyman.

Dourmashkin reported in detail 4 cases of empyema of the ureter. There were no symptoms of irritability of the bladder, and the voided urine, ordinarily purulent, would in some cases be clear temporarily because of closure of the sac. Pus exuding from the ureteral orifice on the nephrectomized side, as seen through the cystoscope, does not necessarily indicate the presence of a dilated ureter filled with pus. In one case a diagnosis of empyema of the ureter was made because of thick pus escaping from the orifice of the ureteral stump. The presence of pus was due to a stone just below the ureteropelvic juncture which was not removed at the time of nephrectomy.

Clinical cure was affected in one case by cystoscopic manipulations. The orifice was enlarged by a fulgurating spark and the sac drained and irrigated with antiseptic solutions. Five years later, examination revealed that the urine was normal and there were no other symptoms.

17. Bugbee, H. G.: Diverticulum of the Ureter: A Report of Three Cases, J. Urol. 26:215 (Aug.) 1931.

18. Dourmashkin, R. L.: Empyema of the Ureteral Stump, J. Urol. 26:553 (Oct.) 1931.

In general, the absence of vesical or other local symptoms which do not indicate a tendency of extension of the infection into the remaining kidney should be left alone.

Draper, Darley and Harvey¹⁹ observed that intramuscular injections of pituitary extract and pitressin reduce the size and density of the pelvic and ureteral shadow, as shown by intravenous urography. The change in pelvic and ureteral visualization is more pronounced as the dosage is increased. With the maximal dose (15 minims) marked diminution in the size and density of the shadows occurs from three to seven minutes after the injection. Since neither pituitary extract nor pitressin when injected intramuscularly produces antidiuresis in the face of diuresis previously induced by iopax administered intravenously, it is concluded that the shadow diminishes due to accelerated drainage caused by active ureteral and pelvic peristalsis and not to antidiuresis.

In a clinical case of pyelitis with bilateral hydronephrosis and hydro-ureter, marked relief of pain followed the exhibition of solution of pituitary, which proved more alleviating than $\frac{1}{6}$ grain (11 mg.) of morphine. It is possible that the clinical improvement noted was due in part to certain changes in the composition of the urine, as brought about by administration of pituitary extract.

Tumor.—Frazer²⁰ reported a case of primary carcinoma of the ureter, which was under observation for four and half years.

Pathologically, ureteral neoplasms are similar to those found in the pelvis of the kidney and the bladder. The types that have been reported are papilloma, benign and malignant, fibroma, papillary carcinoma, squamous cell epithelioma and sarcoma. Primary carcinoma of the ureter is rare. Its presence is suspected in cases of painless hematuria when bloody urine can be seen coming from the ureteral meatus and when the more common conditions are excluded. Varying degrees of obstruction to the lumen cause secondary changes in the kidney. Nephrectomy and complete ureterectomy, combined or as a two-step procedure, is the only adequate treatment. Early diagnosis and radical surgical measures should lower the mortality in these cases, as in cases of operable carcinoma in other parts of the body.

19. Draper, W. B.; Darley, Ward; and Harvey, J. L.: The Effect of Pituitary Extract Upon the Tonus of the Human Pelvis and Ureter and Its Possible Application in the Therapeutics of Pyelitis and Related Conditions, *J. Urol.* **26**:1 (July) 1931.

20. Frazer, E. B.: Primary Carcinoma of the Ureter, *Bull. Mobile City Hosp.* July, 1931.

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SURGICAL TREATMENT OF GOITER

WITH SPECIAL REFERENCE TO THE OPERATIVE TECHNIC *

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AND

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CINCINNATI

There is perhaps no more thrilling story in the history of surgery than man's efforts to relieve sufferers from thyroid conditions. For thousands of years persons with goiter were a perpetual challenge to the skill and ingenuity of physicians. They sought relief from the distressing disfigurement, suffocation, difficulty in swallowing and heart disease. Hundreds of years ago the distress of some of these sufferers caused a few surgeons to discard discretion and to attempt operative removal of goiters when a lack of knowledge of fundamental surgical procedures doomed them to failure in most instances. In the literature there are records of some of these early attempts. It is extremely interesting to read these old records, not only because they recount thrilling and almost blood-curdling stories, but because they show forcibly the advantages that physicians of today possess and the great advances that have been made since that time. They make one realize the duty to posterity to try to continue the great progress that has thus far been made. Almost certainly a hundred years hence surgeons will view the work of today in very much the same light as present day surgeons view the work of a hundred years ago.

The fundamental principles of the technic of operating on the thyroid gland have been fairly well standardized for nearly a quarter of a century. With the use of anesthetics, the introduction of artery forceps and other aids to the control of hemorrhage and the development of aseptic surgery, the efforts of centuries to relieve patients with disfiguring and strangulating goiters began to yield encouraging results. This rapid development began about the year 1883. Prior to this time the textbooks of surgery are uniformly emphatic in their counsel against the foolhardiness of attempting to operate on the thyroid gland. Records show that several hundred attempts had been made before this time, and that the mortality (especially that due to hemorrhage) was frightfully high. To these intrepid pioneers we now point with pride, not because of their results, but because of their failure to yield to a well-

* Submitted for publication, July 14, 1931.

nigh universal opinion. They stimulated an age-old interest that began to bear good fruit as soon as the time was ripe. Between 1883 and the early part of the twentieth century, the fundamentals of the technic of operating on the thyroid gland became established and were employed by the leading surgeons of the world. Since then, many refinements of technic have been made, which have simplified the operation and have reduced the mortality rate to a very low figure.

In 1920, Halsted made this statement:

The control of haemorrhage has always been, as it is today, the chief concern of the operator. Now the surgeon is provided with literally hundreds of artery clamps and the patient being anesthetized there is no need for haste; the operator, unperturbed by the cries or struggles of the patient or the fear of haemorrhage, proceeds calmly and surely from one step of a well perfected method to the next.

At that time he described and illustrated his technic of thyroidectomy.¹ Our modifications of his technic have, we believe, made the operation and the control of hemorrhage easier and have reduced the danger of injury to the recurrent nerves and parathyroid bodies.

TECHNIC

1. The patient is placed on the table without hyperextension of the head and without much elevation of the chin. This position allows the greatest relaxation of the sternocleidomastoid, sternohyoid and sternothyroid muscles; consequently they can be retracted with much greater ease. The gland can also be delivered out of the wound much farther and much more easily. The advantages of this relaxation more than compensate for the apparent hole in which one has to work.

2. A straight collar incision is made high enough so that the resulting scar will be above the inner ends of the clavicle. This is usually determined by marking the skin while the patient sits up and holds the head slightly flexed. In this way the scar can often be placed in a natural wrinkle of the neck. A scar that comes over the ends of the clavicle and manubrium is usually conspicuous and unsightly.

3. The skin and divided platysma muscle are retracted, exposing the thyroid cartilage above and the suprasternal notch below. This can usually be done without injury to the external and anterior jugular veins. We believe that the division of this muscle and its careful resuturing lessen the ultimate width of the scar. Certainly the careful suture of the platysma muscle allows an early removal of the skin sutures, and thereby avoids the danger of the cross-marks. Our skin sutures are removed at the end of forty-eight hours.

4. The sternohyoid muscles are separated in the midline from the thyroid cartilage down to the sternum. For many years we have not found it necessary to divide these muscles.

5. The sternohyoid muscles are separated from the sternothyroid muscles back to the neurovascular bundle on each side. This can be done very easily, by blunt dissection and usually without the necessity of tying a blood vessel. When this is done, one can break through the thin fascia at the posterior margin of the sternothyroid muscle and thus completely free the posterior part of the superior pole.

1. Halsted: *John Hopkins Hosp. Rep.* 19:71, 1920.



Fig. 1.—The line of incision marked so that the scar will be in one of the normal wrinkles of the neck. Note that it is placed well above the ends of the clavicle.

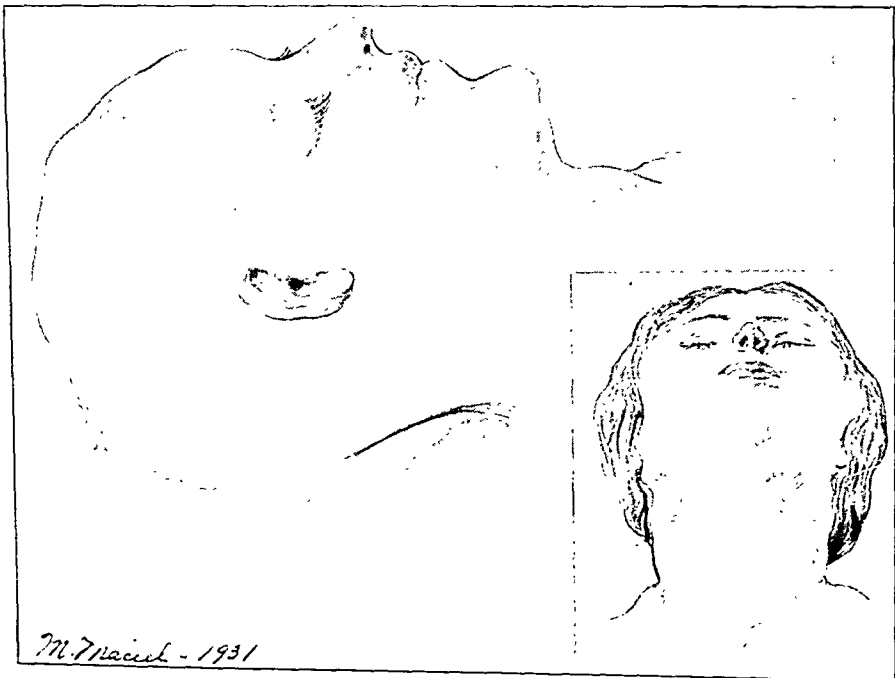


Fig. 2.—The position of the head, as compared to the position of extreme extension often employed.

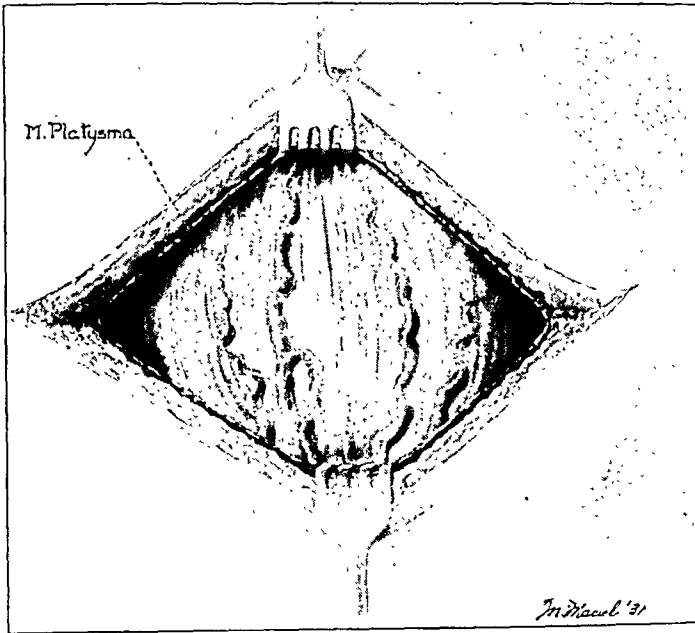


Fig. 3.—The subcutaneous tissues and platysma dissected free from the subjacent structures and retracted upward and downward.

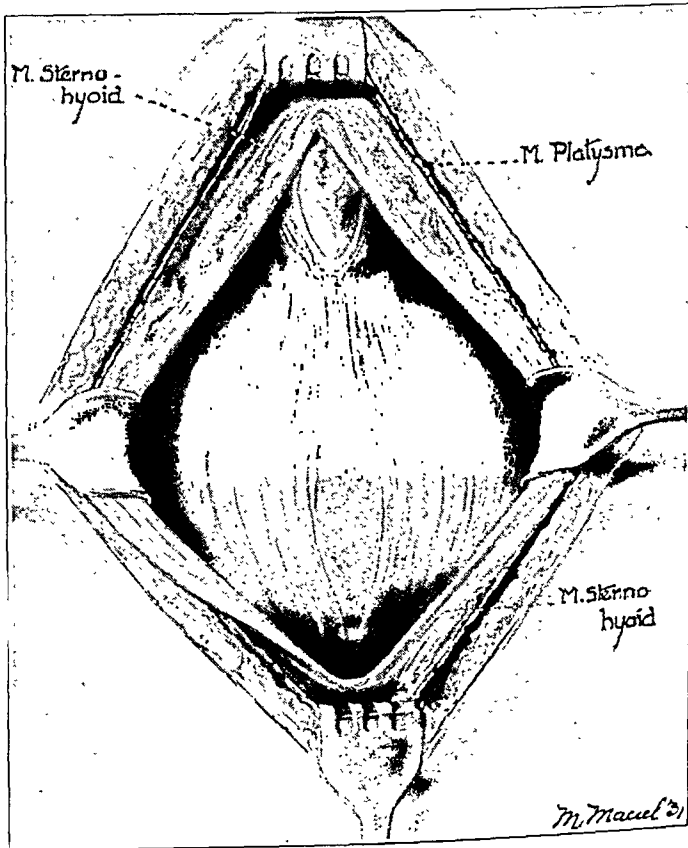


Fig. 4.—Vertical incision between the sternohyoid muscles, which are then freed from the sternohyoid muscles as far posteriorly as the neurovascular bundle on each side.

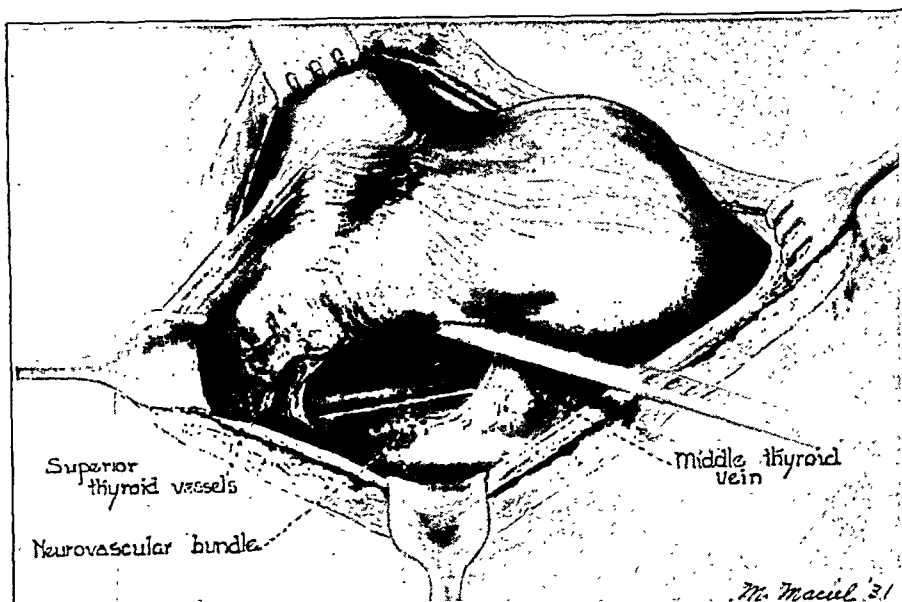


Fig. 5.—Breaking through the fascia between the neurovascular bundle and the posterior aspect of the upper pole of the thyroid before freeing the sternothyroid muscle from the gland.

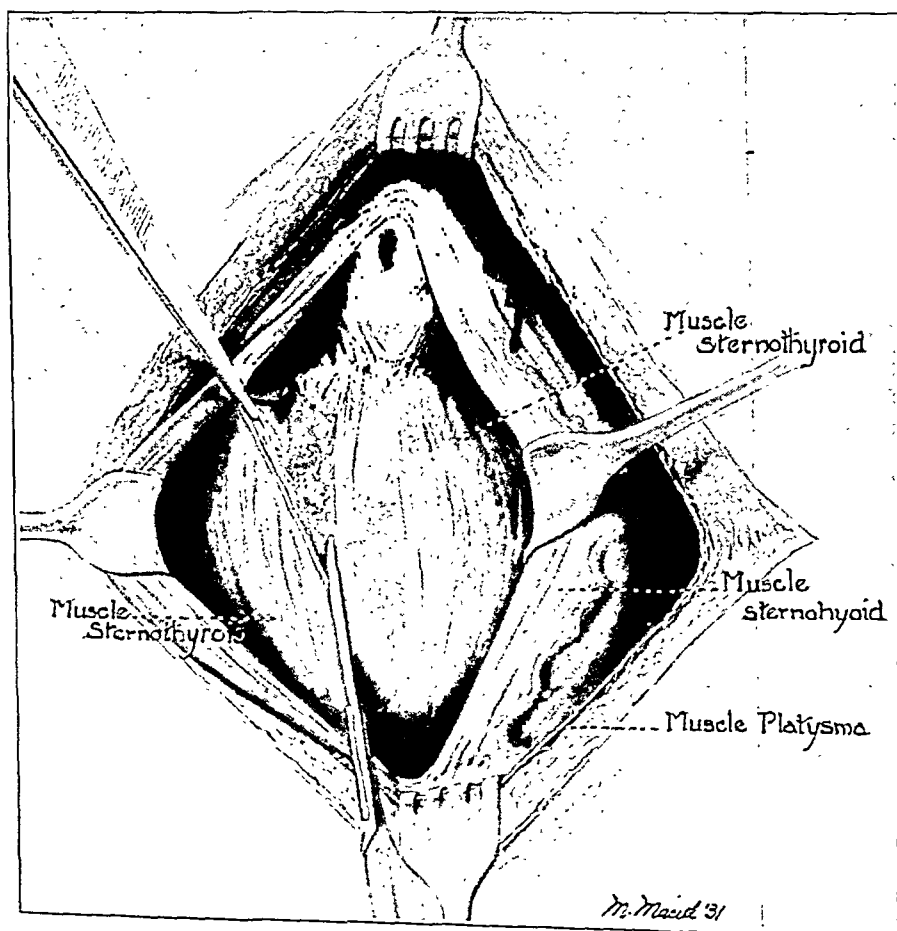


Fig. 6.—Incision along the anterior border of the sternothyroid muscle.

One should not attempt this except at the upper pole, for at the middle of the gland and lower the veins that run from the thyroid over to the jugular vein may easily be injured.

6. The sternothyroid muscle is split, freed from the gland and retracted under the sternohyoid muscle, which has previously been slid under the sternomastoid muscle. In the freeing of this last muscle it is helpful to get as close to the thyroid gland as possible without injuring it or its vessels.

Anatomic studies show that the freeing of these two muscles paves the way for a much easier and wider exposure of the thyroid gland. It allows both the

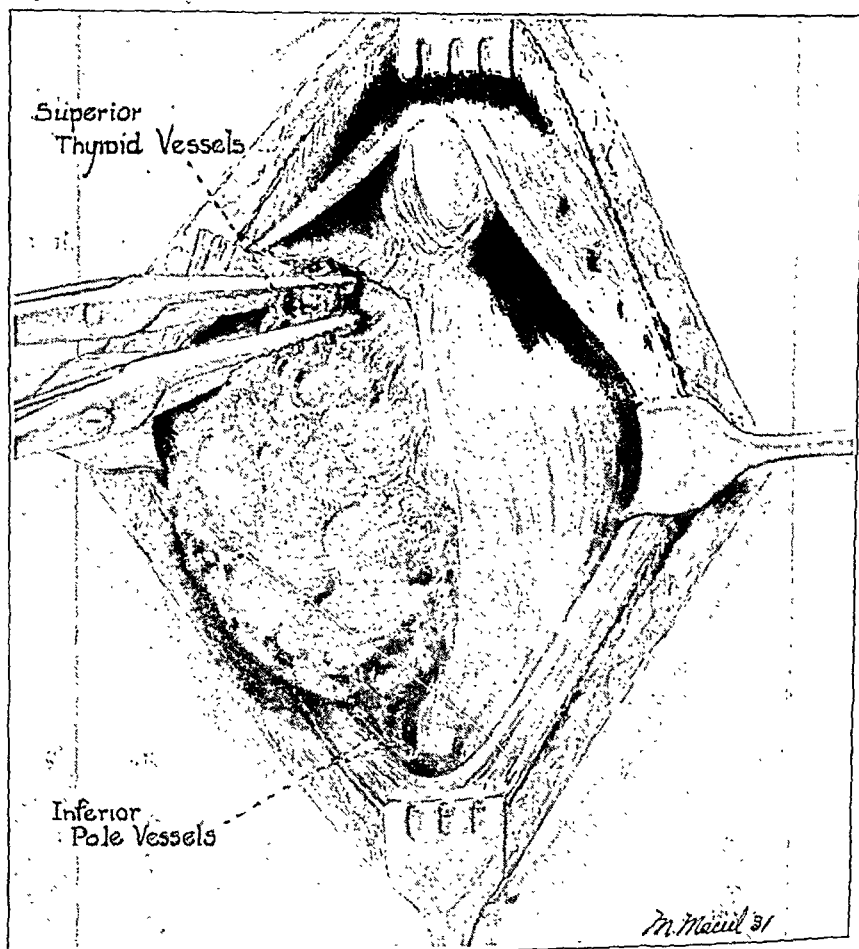


Fig. 7.—The sternothyroid muscle freed from the gland, the upper pole delivered and its vessels grasped with clamps.

sternohyoid and sternothyroid muscles to slip easily under the sternocleidomastoid muscle, whereas if it is not done, the binding fascial planes prevent their wide retraction.

7. After the upper pole is freed far posteriorly, the finger is slipped behind and above it. The upper pole is then delivered downward and forward into the wound so that its vessels can be easily clamped.

8. The superior pole vessels are then divided and the upper end of the thyroid gland freed from the trachea.



Fig. 8.—The upper pole vessels divided between clamps, and the fascia between the anterior aspect of the upper pole and the trachea divided.

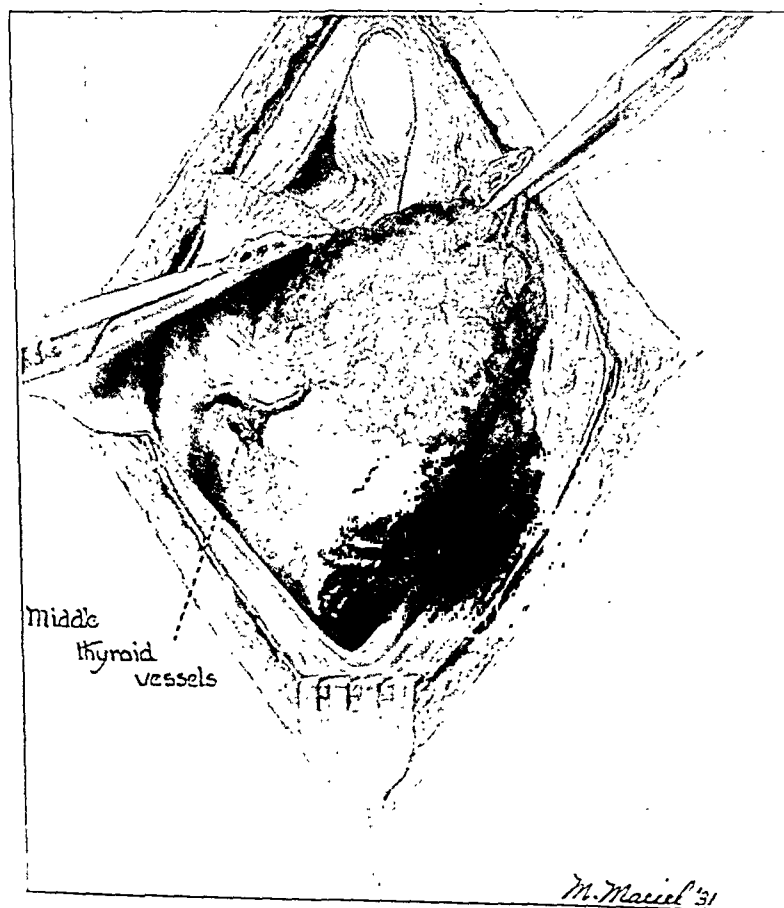


Fig. 9.—The right lobe rotated anteriorly, showing the vessels extending from the jugular vein to the middle of the gland.

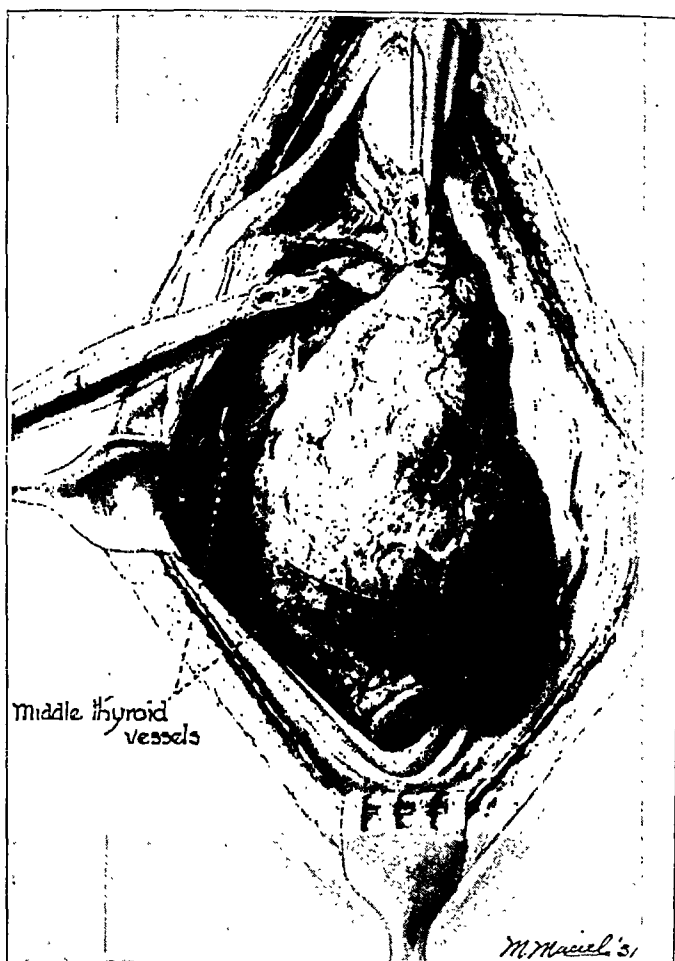


Fig. 10.—Showing the rotation possible after the division of the vessels shown in figure 9. The dissection has been carried behind the lobe.

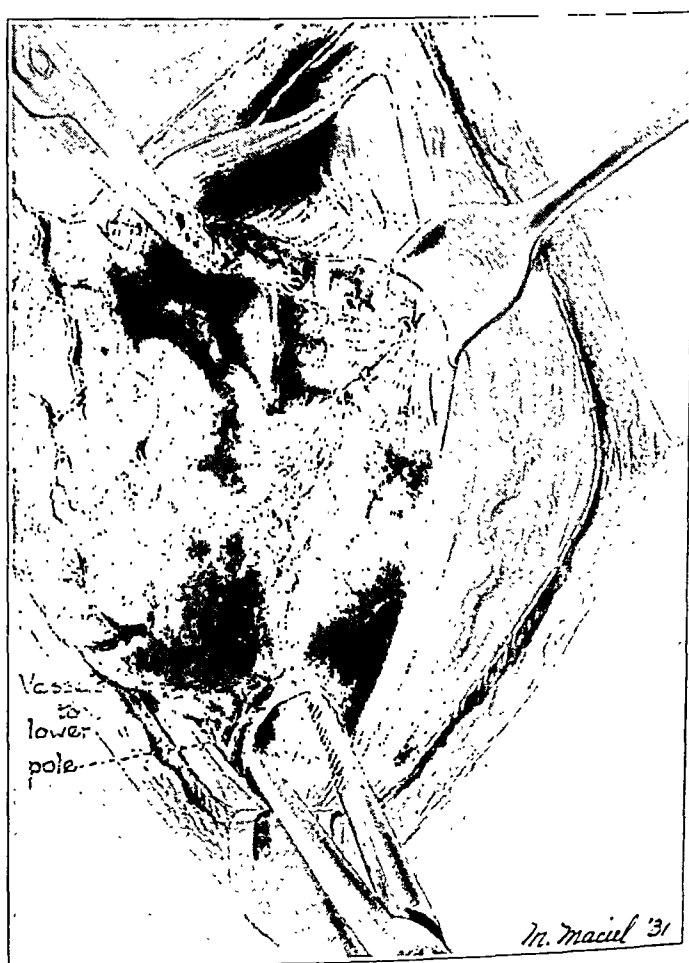


Fig. 11.—Exposure of the trachea at the lower margin of the isthmus and mesial to lower pole vessels.

9. By pulling the divided end of the thyroid gland across the trachea and upward, the middle portion of the gland and lower pole can easily be freed back to the trachea and lifted into the wound. In this step it is essential to ligate the vein or veins that run from the gland out to the jugular vein. By staying close to the gland, the recurrent nerve is freed and allowed to drop back away from danger of the further steps of the operation.

10. With blunt forceps, the trachea just below the isthmus is exposed.

11. The inferior thyroid vessels are then clamped and divided just after their entrance into the gland.

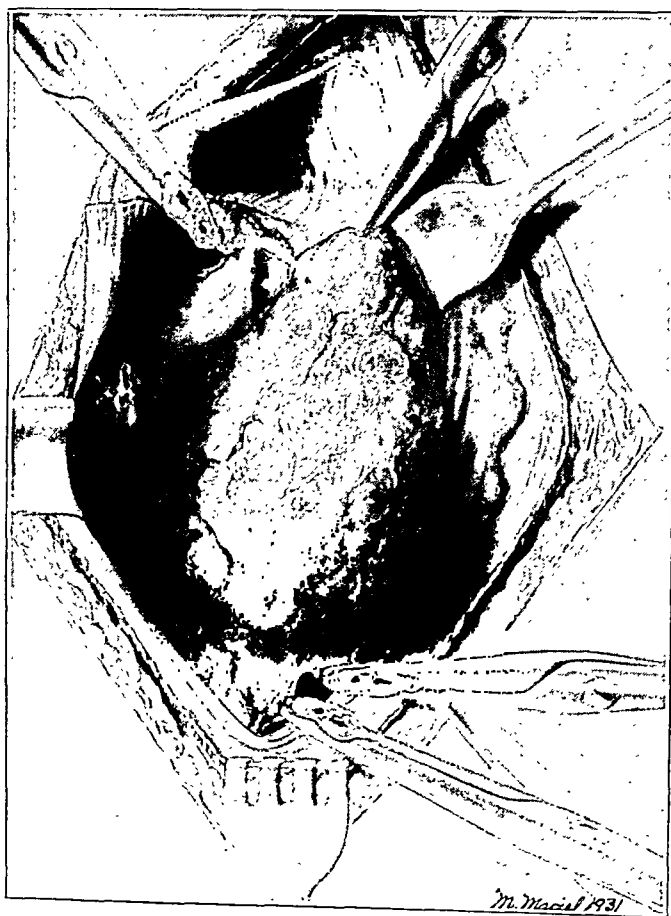


Fig. 12.—The lower pole vessels grasped and divided between clamps; the lateral branches remain to supply the portion of the gland not removed.

12. The superior and inferior poles of the lobe are next held upward and mesially, allowing the application of clamps along the posterior part of the gland. The line of application of these clamps is determined by the amount of gland that should be left.

13. The gland is divided, just distal to the row of clamps, to the anterior wall of the trachea. In the application of additional clamps, we try to clamp the individual vessels in order to avoid damaging the thyroid tissue.

14. The isthmus is next freed from the trachea. At this point the operation is halted until all vessels on this first side are carefully transfixed and ligated with

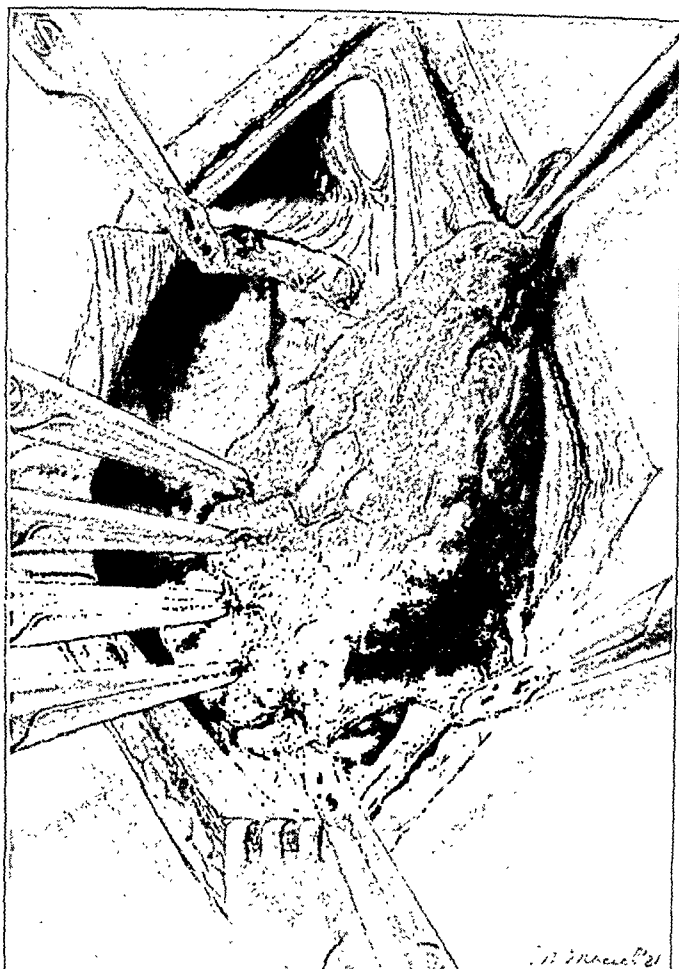


Fig. 13.—The lobe retracted strongly across the midline—clamps applied to the vessels of the capsule along the anterior margin of the portion to be left behind.

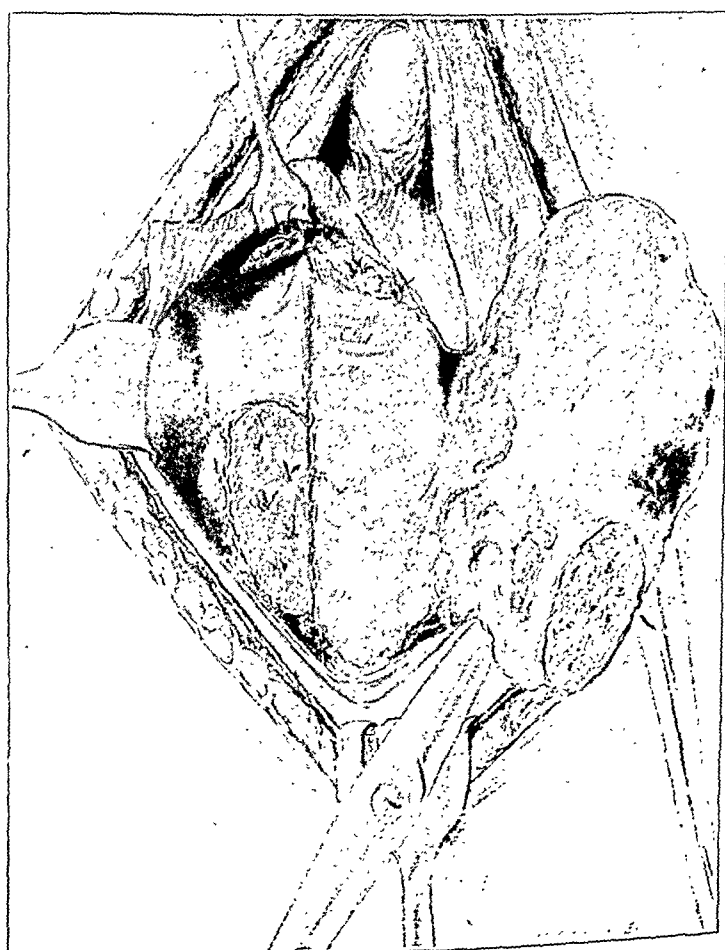


Fig. 14.—The right lobe removed, the vessels ligated and the left lobe freed from the anterolateral aspect of the trachea.

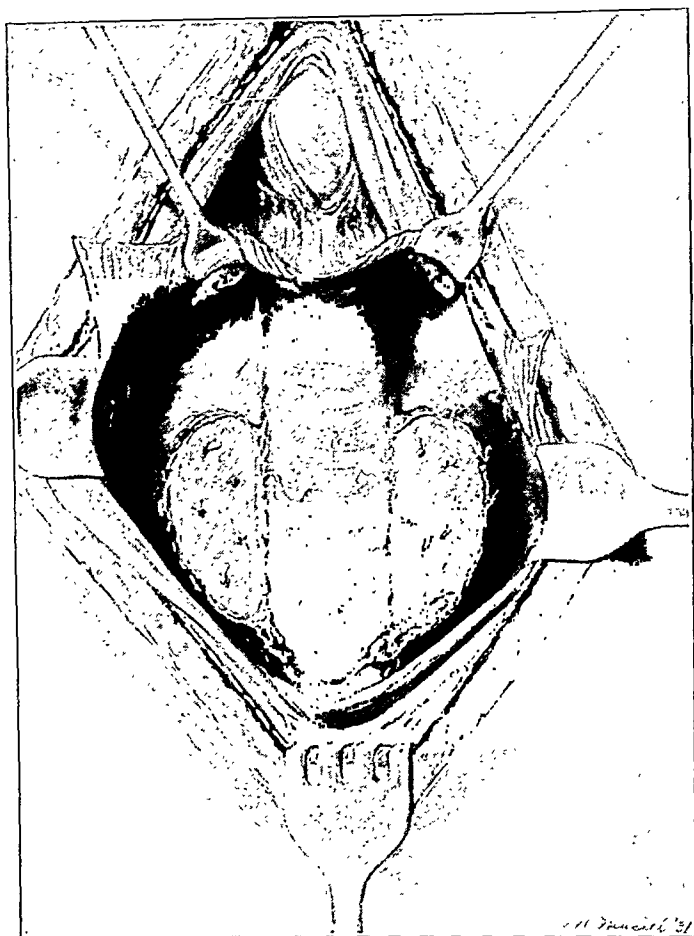


Fig. 15.—The excision completed—all vessels ligated—showing the position and approximate size of the portions left behind.

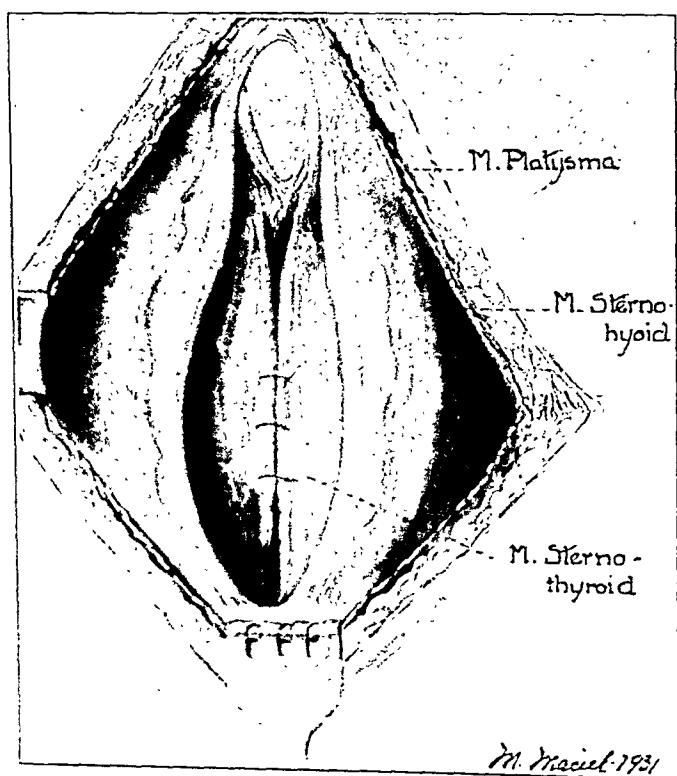


Fig. 16.—The closure begun. The sternothyroid muscles loosely approximated in the midline with interrupted sutures.

silk. This procedure not only eliminates the use of many clamps, but allows one to see exactly how large a portion of the gland has been left on this side. In this way, one can judge more accurately just how much gland should be left on the other side.

15. The operation on the opposite side is then performed in exactly the same manner, except that traction on the freed isthmus makes the procedure easier.

16. The retracted muscles, the cut platysma and the skin are then sutured loosely with interrupted fine silk sutures. In some cases, a soft rubber protective drain is used for twenty-four hours. When this is done, an untied skin suture is left in place to be tied when the drain is removed. With this procedure, the site of the drain is never visible.

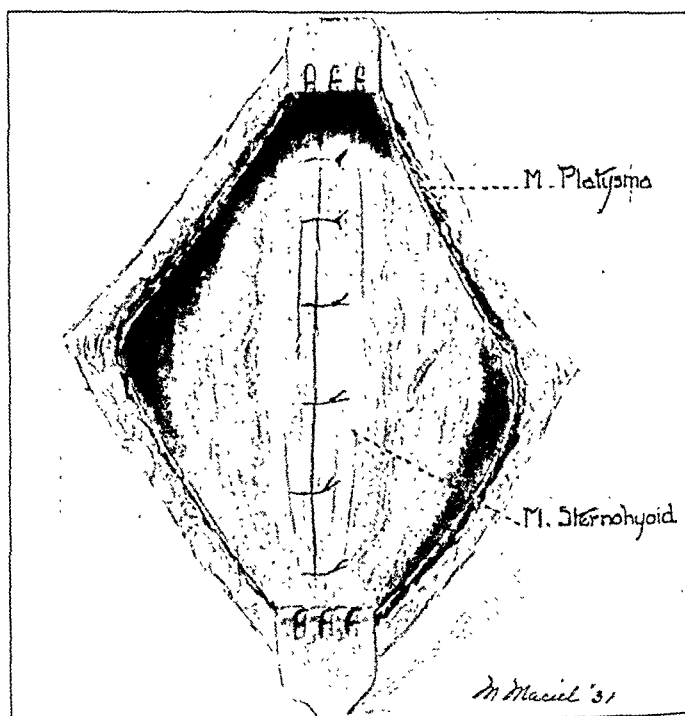


Fig. 17.—Suture of the sternohyoid muscles.

COMMENT

The aforementioned operation is the typical procedure for an exophthalmic gland. However, the essential features of it are employed in all types of goiter. It is usually the easiest method of delivering sub-sternal goiters, and it is equally applicable to the nodular and adenomatous type of gland.

Of tremendous importance is the amount of gland that should be left and the procedure is often slightly modified to meet the requirements of the judgment of the operator in this respect. In the typical exophthalmic case, we leave no thyroid tissue at either the superior or inferior poles, for we believe that to do so increases the risk of recurrences. In

such cases, we also leave a relatively small posterior strip of gland along the side of the trachea. With the introduction of the use of compound tincture of iodine and the consequent great reduction in the size of the gland before operation, we are leaving less of the gland than we formerly did. The small amount that is left probably increases in size to the amount that it was before the use of compound tincture of iodine solu-

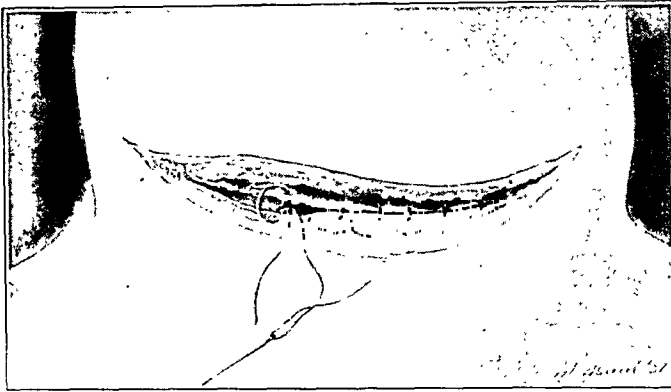


Fig. 18.—The suture of the platysma, the knots thrown inside of the muscle.

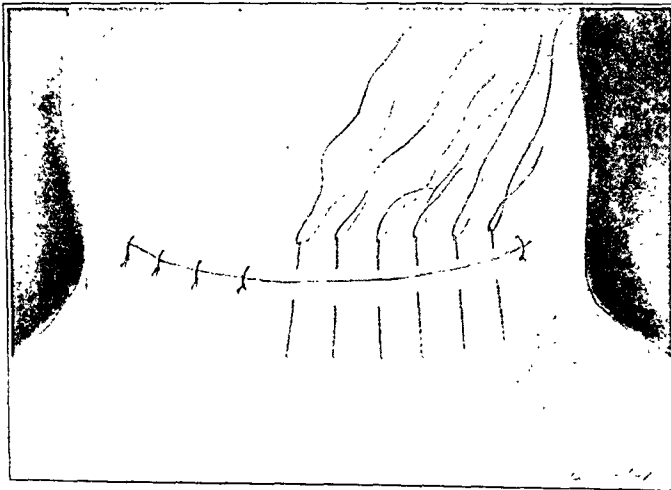


Fig. 19.—The skin sutures being placed.

tion was begun. In nodular goiters in which it may be desirable to leave as much apparently normal gland as is possible and in which the danger of recurrence is less, we leave thyroid tissue at both poles as well as along the side of the trachea. We almost uniformly perform a bilateral resection of both lobes in cases of nodular goiters instead of enucleating adenomas.

Preoperative Preparation.—It is difficult to give any definite routine, for some slight variation in preoperative treatment is usually demanded

by each patient. However, we shall discuss briefly some of the more important things that we do.

1. Rest prior to operation is essential. The duration of this varies with the toxicity of the patient and his response to the preoperative therapy, but we insist that every one, even in the apparently nontoxic cases, has a certain amount of absolute rest.

2. Compound tincture of iodine is given in every case. The amount varies from 10 to 20 minims (0.6 to 1.25 cc.), four times a day. The obviously toxic patients receive the largest doses. Here, also, the duration of this therapy varies with the toxicity of the patient and his response to the drug. Usually between five days and two weeks one gets the impression that this drug has had its optimum effect. The response to its use is always more satisfactory if the patient has not

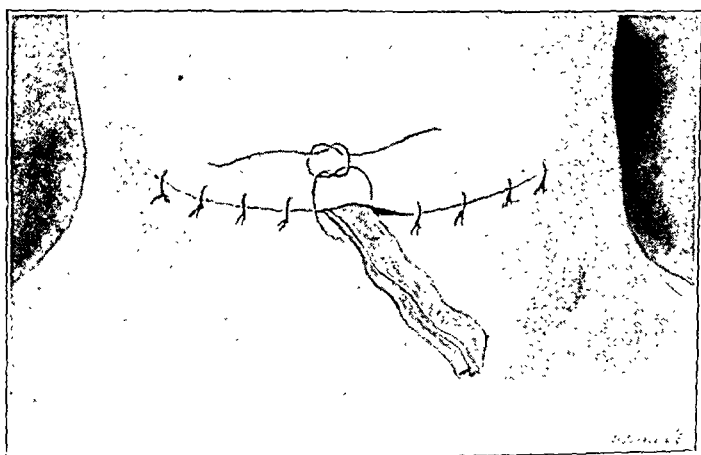


Fig. 20.—Showing the site of the drain, with suture placed, but left to be tied after removal of the drain in twenty-four hours.

previously been receiving compound tincture of iodine. Indeed, some of our very sick patients, who have been taking the medicine for a long time, seem to do better and to get in better condition for an operation by omitting its use entirely. In the nontoxic or relatively mild cases, we permit the patients to take the medicine at home for several days before entering the hospital and thus shorten the period of preoperative preparation in the hospital.

3. One grain (0.065 Gm.) of phenobarbital is usually given three times a day. More or less may have to be given, depending on the excitability of the patient and the susceptibility to the drug. At any rate, enough is given to make the patient sleep a great deal. At 10 o'clock the night before the operation, 3 grains (0.195 Gm.) is given, and the dose is repeated one hour before operation. In addition, $\frac{1}{4}$ grain (0.0162 Gm.) of morphine sulphate is given one-half hour before the operation.

4. Patients with nodular goiters and all patients with thyroid conditions beyond the age of 40, are given digitalis before operation whether or not there is an irregularity of the heart action. We do this so that the patient will have in his system a considerable amount of this drug during the first forty-eight hours after operation, for one cannot foretell in what case a distressing auricular fibrillation will develop during this period. In many cases, particularly the long-standing ones, a perfectly regular heart action prior to operation will be found and then suddenly an irregularity will develop afterward; in such cases, it is a comfort to have the patient at least partially digitalized. We think that any patient, regardless of age, who has weathered a long storm of hyperthyroidism should be given from 15 to 25 grains (0.972 to 1.62 Gm.) of this drug. It is given during the four or five days before operation, and the amount is gaged by the size and weight of the patient and his response to or toleration of it.

5. Food and fluids should be given most freely. Carbohydrates are the best food. We encourage our patients to eat candy, and this suggestion often brings a look of surprise, for many of them have denied themselves sweets for a long time. We often set a limit of from 3,000 to 5,000 cc. on the fluid intake. If a patient does not cooperate in this respect, a large subcutaneous injection of salt solution not only does good but usually insures cooperation thereafter.

6. The patient's mental attitude should be carefully prepared for the operation. Minimizing the danger of the operation and stressing the good that it will do helps a great deal. Pointing out the gloomy future, but for the operation, often gives him a different point of view. We often say that he is lucky the heart trouble is due to a goiter. When one has instilled into the patient a feeling of absolute confidence, when one has made him eager for the operation in the hope of relief, a good job of psychotherapy has been done.

7. One's general impression of a patient's condition is often a most valuable guide as to his preparation for operation. Disappearance of an anxious and strained expression, loss of fear and a steady pulse rate mean a great deal more to us than a drop in the basal metabolic rate. On the other hand, a great drop in the metabolic rate without a calmness of temperament and lowering of the pulse rate will not make us decide to operate. We rely so much on these general evidences of a patient's preparation for operation and so little on the fall in the metabolic rate that we seldom make the latter determination after preoperative preparation has been begun.

Anesthetics.—We are strong advocates of local anesthesia but do not insist on it unless the patient is so toxic or has such a bad heart that we think a general anesthetic will make a real difference in the con-

valescence. We employ local anesthesia in more than 90 per cent of our cases and are convinced that the convalescence is easier and the reaction less severe than after a general anesthetic. In a recent talk with Crile, he expressed the belief that a general anesthetic could not help depressing or affecting one's vital processes. When we do use a general anesthetic, nitrous oxide alone nearly always suffices. We have tried avertin, but we do not like it. Some of the operators in the General Hospital however, are, still giving it a trial.

Postoperative Treatment.—During the first forty-eight hours the patient is kept very quiet and in a semireclining position. Morphine is used freely if necessary. Phenobarbital is given if there is no nausea. Not infrequently, patients with hyperthyroidism will be nauseated by morphine; in such cases, a mixture of opium alkaloids may be tolerated more easily.

Fifteen minims (0.92 cc.) of compound tincture of iodine is given every four hours until we are sure that the patient has passed the peak of the reaction. This usually occurs in the second twenty-four hours. After that the amount is reduced gradually and is usually discontinued in from four to ten days. We give it by mouth, but whenever any given dose is vomited, three times the amount is immediately given by rectum.

The amount of the fluid intake is kept very high and is given by mouth or subcutaneously if necessary. In almost all toxic cases the patients are given from 2,500 to 3,000 cc. of physiologic solution of sodium chloride subcutaneously immediately after operation. A patient who has taken the maximum quantity of fluids, compound tincture of iodine and digitalis is much less likely to have a so-called thyroid crisis and is much better able to stand a serious reaction if this should ensue. Nourishment, particularly carbohydrates and fluids, is given freely by mouth as soon as there is no nausea. The pain of swallowing is not considered an excuse for not taking them.

One half of the stitches are removed after twenty-four hours and the rest between forty-eight and seventy-two hours after the operation.

The patient is watched at intervals for several months and is given definite instructions as to what to do with regard to diet, exercise, rest, the avoidance of excitement, etc. In this period, we often bargain with patients. For instance, we may tell them that they can begin to smoke, drink coffee or do other things after they have gained a certain number of pounds in weight.

Complications.—The aforementioned postoperative treatment takes care of practically all cases, but does not provide for the complications. We shall make mention of a few of the most important ones. Hemorrhage occasionally occurs even when the operations are done by the most skilled surgeon. Doubly ligating the pole vessels and making the patient cough violently before closing the wound, in order to test any vessels

that are not properly ligated, will make postoperative hemorrhage a rare occurrence. Drainage of the wound is not a safeguard against bleeding, for if it occurs, the wound will fill up and cause distressing symptoms even when a drain is inserted. If the nurses and assistants are trained to watch the contour of the patient's neck and the ease of breathing, such hemorrhages can usually be detected very early. When hemorrhage does occur, the wound should be reopened immediately and the bleeding stopped. If this is done early enough, the wound can usually be reclosed exactly as it was at the primary operation.

Respiratory distress is rare, but it does occur. It may be caused by injury of the recurrent nerves at the time of operation, or it may

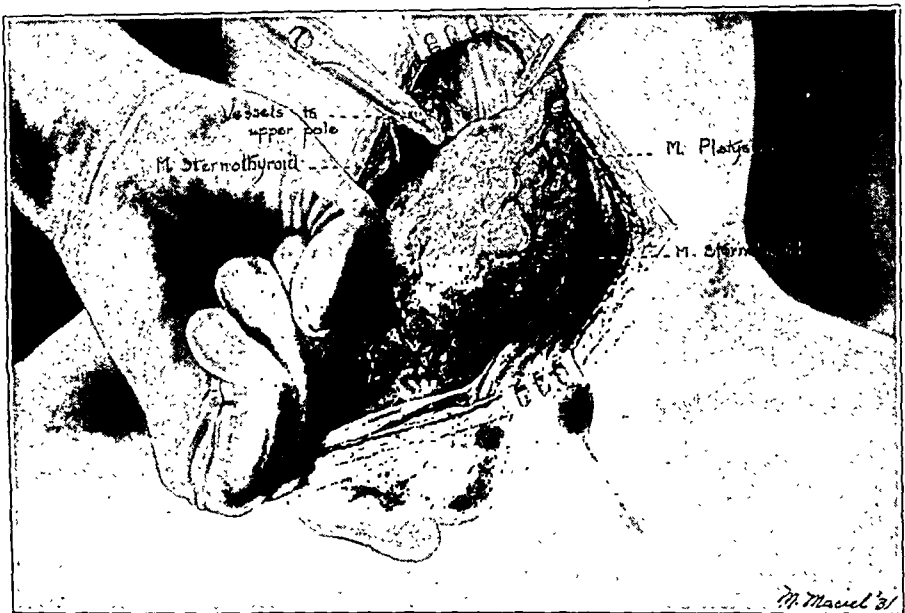


Fig. 21.—Showing delivery of a subternal goiter and indicating the importance of continuing the dissection in the plane closest to the gland.

occur later as a result of irritation or temporary paralysis of them owing to edema, etc. Our belief is that the so-called collapse of the trachea never occurs; the condition is always due to a disturbance in function of the recurrent nerves. When this complication arises, the respiratory obstruction throws a great strain on the patient's convalescence. It is a particularly heavy burden to a patient with a cardiac condition. Although we have never had to do it, we would not for a moment hesitate to perform a tracheotomy in order to relieve the patient of the work of trying to get air. We are sure that the tendency in such cases is to wait too long in the hope that the trouble is due to a temporary paralysis of the nerves and will pass off with a subsidence of the wound reaction. The exhaustion from respiratory labor may be enough to

make the difference between recovery and death. Early tracheotomy adds only the complication of a mild wound infection and relieves the exhaustion of respiratory obstruction. If the obstruction is temporary, the tracheotomy wound heals promptly after its disappearance; if permanent, the tracheotomy wound will have to be permanent. If the tracheotomy is done after the patient is completely exhausted, it may be too late to avert death.



Fig. 22.—Cross-section of the neck, showing on the left the plane of dissection of the posterior surface of the sternohyoid muscle, and on the right, the degree to which the sternohyoid and sternohyoid muscles may be retracted after this dissection has been carried out.

The first symptoms of tetany should be detected. Restlessness, inability to sleep and occasional double vision are enough to warrant the making of a blood calcium determination. If the blood calcium is 8 mg. or less per hundred cubic centimeters, one is justified in giving calcium lactate by mouth. Early treatment will avoid the necessity of intravenous therapy and the consequent danger of calcium chloride spread-

ing into the tissues. Trousseau's or Chvostek's signs are warnings of impending convulsions, but even if these are detected early, intravenous therapy and the use of parathormone can usually be avoided. In a recent case in which the goiter was retrotracheal, the patient complained of occasional double vision on the fourth day and held her thumbs slightly pulled in toward the palms. The blood calcium was 7 mg. One drachm of calcium lactate four times a day and ten drops of viosterol three times a day completely relieved the symptoms. These doses were gradually reduced to three a day, without symptoms, but when completely discontinued on the tenth day, the symptoms returned. It is too early to tell whether this is a temporary disturbance to the parathyroid bodies or whether she will have to continue the medication indefinitely. We are sure that early recognition of the symptoms avoided urgent measures for treatment. In any case, the treatment should be withdrawn as soon as possible, in order to stimulate the development of any parathyroid tissue that may be left. Experimentally, the least portion of parathyroid tissue left behind, or even transplanted into some other part of the body, will grow and furnish ultimately an adequate secretion if the animal is deficient in parathyroid secretion. As soon as patients with tetany learn to recognize the characteristic feelings and signs of the condition, they can be trusted to reduce the dosage of their medicines, for at the first evidences of its return, there is no question but that they will begin the medication or increase its amount. The general feeling of the patient with tetany must be a distressing one.

When we have not been successful in anticipating and preventing a so-called thyroid crisis, we employ the following measures: 1. Absolute rest. Strong sedatives are necessary, such as morphine, opium alkaloids and paraldehyde. The dosage required is much more than the average; the amount necessary can be judged only by the effect that is obtained. Some authorities give amytal intravenously when other sedatives have failed to give rest. 2. Great quantities of physiologic solution of sodium chloride and solutions of dextrose are given subcutaneously and intravenously. 3. Compound tincture of iodine is given in large doses. 4. Five cubic centimeters of a 10 per cent solution of sodium iodide is sometimes given intravenously. 5. The patient is immediately put into an oxygen tent or chamber. This procedure reduces markedly the work of breathing, which would otherwise be necessary to meet the demands of the great increase in metabolic processes. 6. The patient is kept fully digitalized. If this is partially or completely done prior to operation, it is necessary only to supply a small daily amount. Some operators give 0.0008 Gm. of strophanthin, U. S. P., intravenously. In every case the advice of a cardiologist should be secured. 7. The administration of thyroxine has been employed by Rogers and others. Our limited experience with its use does not allow us to comment on its value.

AN OSTEOLASTIC OSTEOD TISSUE-FORMING TUMOR OF A METACARPAL BONE *

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Benign tumors of the short tubular bones of the hands and feet are relatively frequent. Malignant tumors occur rarely, and adequate information is not available to permit a full discussion of the nature of such lesions, or to draw conclusions concerning their clinical course and prognosis. We have observed a tumor of the fourth metacarpal bone that seems to be of interest clinically, roentgenologically and pathologically.

REPORT OF A CASE

The patient (C. Z.) was a girl, 15 years of age when she first came under our care. She had noticed a swelling in the region of the fourth metacarpal bone of the left hand in March, 1927, when she was 12 years of age. At first the enlargement was not great, but pain on pressure was present. Roentgen examination at that time showed expansion of the diaphysis of the fourth metacarpal bone by a tumor extending from the base of the bone to the epiphyseal cartilage plate; the expansion was fairly symmetrical. The lesion was predominantly osteoclastic, but irregular zones of what appeared to be new bone formation could be observed throughout the lesion. The surrounding soft tissues were not invaded by the tumor, but a portion of the fifth metacarpal bone contiguous to it showed cortical and periosteal thickening (fig. 1). A biopsy was performed at another hospital in March, 1927, and in December, 1929, after the patient came under our observation, we obtained the slides prepared from the excised tissue.

Clinically, there was no great change until about July, 1929, when the tumor began to grow rapidly. At this time roentgen examination showed that the entire metacarpal bone was involved in the pathologic process. The distal half of the bone was sclerotic, and calcific changes predominated. There was marked soft tissue swelling, as shown by a mass on the dorsum of the hand (fig. 2).

During the next six months the lesion progressed rapidly, the hand enlarging considerably, and in December, 1929, the patient was first admitted to our hospital. She was a well developed and well nourished bright young girl, about 15 years of age, and presented no abnormalities except for the lesion in the left hand, which had existed for almost three years. This was a hard tumor, but was not painful, and the skin over it was tense. The fourth and fifth fingers were held in flexion, and extension was not possible. Urinalysis and a Wassermann test of the blood gave negative results. The lymph nodes showed no enlargement.

* Submitted for publication, July 11, 1931.

Roentgen examination showed that practically the entire shaft of the metacarpal bone had been destroyed. A small portion, restricted to the head with its cartilaginous covering, still persisted. The soft tissue swelling had progressed considerably since the last roentgen examination, in July, 1929. Bone production in the soft tissues was much more pronounced and characteristic than on any of the previous plates, and was predominantly transverse to the long axis of the shaft. The shafts of the fifth and third metacarpal bones were displaced by the mass; some degree of periostitis was noted along the shaft of the third metacarpal bone, while the shaft of the fifth metacarpal bone showed irregular atrophy. The



Fig. 1.—Roentgenogram showing the expanded diaphysis of the fourth metacarpal bone in March, 1927. Note that the epiphysis is free from disease.

lungs, ribs and lower extremities showed no metastatic foci. The conclusion reached by Dr. Pomeranz, the roentgenologist, was that the lesion was a malignant tumor of the metacarpal bone, probably an osteogenic sarcoma (figs. 3 and 4).

On Dec. 18, 1929, the patient was operated on by one of us (Dr. Mayer), who made a 17 cm. incision on the dorsum of the left hand in the line of the fourth metacarpal, excising an ellipse of skin 2 cm. wide. Immediately beneath the skin was found the smooth, well encapsulated surface of the tumor mass. This was dissected free from the extensor tendons, and the dissection was carried toward the palmar surface. The tumor was found densely adherent to the fifth metacarpal, and was slightly adherent to the third metacarpal bone, from which it was readily separated by a chisel. The mass was disarticulated from the proximal phalanges

of the fourth and fifth fingers, care being taken not to injure the tendons of these fingers. On the palmar surface, it was enucleated without any appreciable damage to the tendons or the nerves. The removal of the tumor was apparently complete.

To fill the gap left by the removal of the tumor a tibial bone graft, about 13 cm. long and 3.5 cm. wide at one end and 2 cm. at the other, was wedged firmly



Fig. 2.—Further involvement of the bone in July, 1929. Note that the former epiphyseal region is now involved.

between the carpal bones and the phalanges, the narrow end being proximal. To give support to the fifth finger, a small shoulder was cut on the ulnar half of the graft. The wound was closed with no. 3 chromic catgut, an interrupted suture for the interossei and a continuous stitch for the fascia. The extensor tendons of the fourth and fifth fingers showed a marked laxity, due to the extreme stiffening caused by the tumor. They were therefore divided and overlapped by the button-



Fig. 3.—Note the marked enlargement of the tumor in December, 1929. The articular cartilage is seen. The dense shadow is caused by the newly formed bone and calcified osteoid tissue.

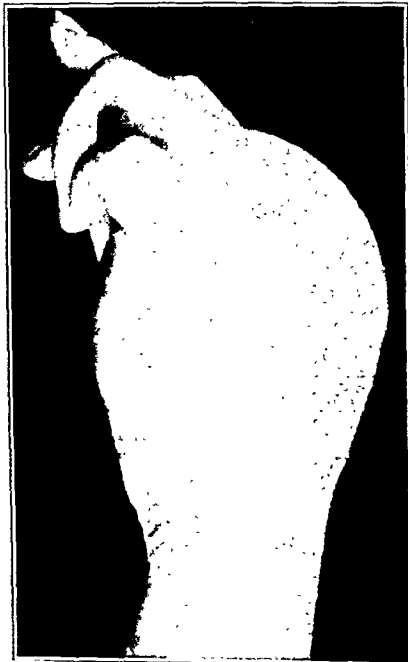


Fig. 4.—Appearance of the hand before operation, in December, 1929.



Fig. 5.—Roentgenogram of the hand, bone graft in situ, in June, 1931.

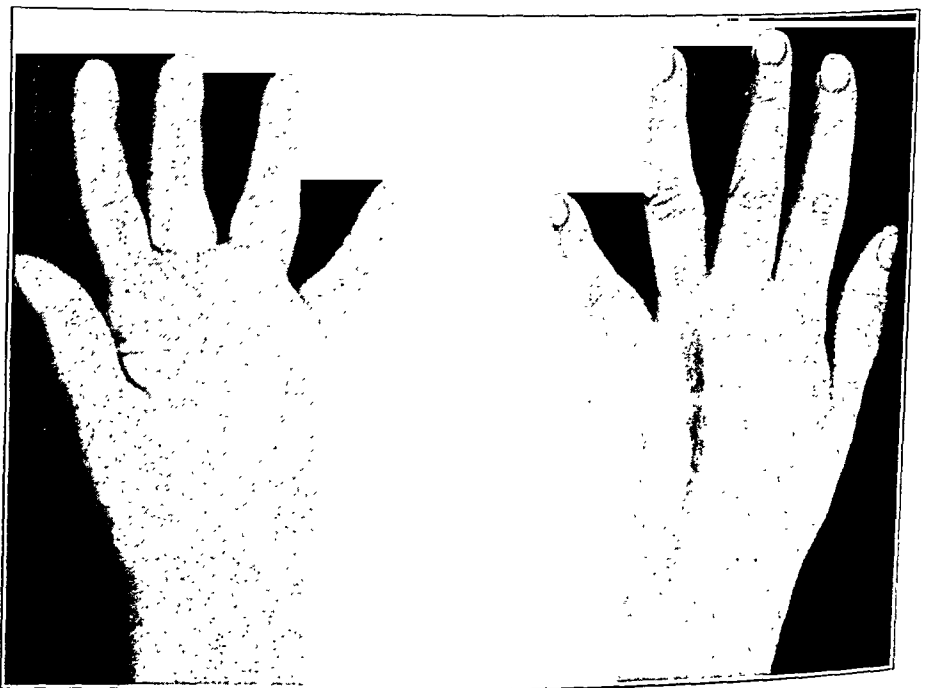


Fig. 6.—Appearance of the hand in June, 1931.

hole method, so as to take in the slack. Five or six sutures were taken, holding the tendons together. The skin was closed by subcutaneous and continuous stitch of no. 00 plain catgut. The hand was immobilized in a plaster of paris splint, in slight hyperextension.

The operative wound healed by primary intention. The patient has been seen at regular intervals. Up to the time this paper was written (June, 1931), there has been no sign of recurrence, either local or general, and the patient has gained 25 pounds (11.3 Kg.) in weight. She has excellent function of the thumb and the index and middle fingers; the little finger has about 25 degrees of motion. The fourth finger is ankylosed to the bone graft. Further operative procedures are planned to give increased motion to the fourth and fifth fingers (figs. 5 and 6).

Pathologic Examination.—The tumor when removed measured 10 by 6.5 by 6 cm. It was covered by a thin fibrous capsule which was almost completely intact,



Fig. 7.—The tumor. Note the numerous small cysts.

a few rents being produced during its removal. The fifth metacarpal was extremely flattened, but lay completely outside the capsule. Its cortex was of irregular thickness, and showed the proliferation of periosteal bone on one surface, apparently the result of pressure irritation.

The tumor was of such consistency that it could be cut with a knife, but it was quite granular and firm. There was a peripheral zone, about 1 cm. in width, which was whitish and gritty like osteoid callus. The inner portion of the tumor was yellowish white or pinkish in appearance. Within the substance of the tumor a small dense bony area was found, which consisted of calcified and ossified osteoid tissue and newly formed bone. This area produced the dense shadow seen in the roentgenogram. Near it a small piece of articular cartilage was observed, the remains of the fourth metacarpal bone. The cut surface of the tumor showed a number of cysts, most of which measured only a few millimeters in diameter, but one large cyst 2 cm. in diameter was also present. Most of the cysts were lined with a thin membrane (fig. 7).

Pieces of the tumor were fixed in a solution of formaldehyde. To assure easy sectioning, these were decalcified in Mueller's fluid. The paraffin sections were stained by the following method: hematoxylin-eosin, van Gieson, Mallory's aniline blue, a modification of the Weigert fibrin stain and Foot's modification of the del Rio Hortega stain. Some fixed but undecalcified tissue was stained by the von Kossa and alizarin methods.¹

Histologic examination indicated that the tumor arose from cells capable of forming osteoid tissue and bone. The histologic picture was not uniform, as the lesion showed multiple foci of origin, and the process revealed different degrees of development in the various portions of the tumor. The least differentiated portions of the tumor were quite cellular and the cells seemed to be osteoblasts, though the methods of fixation and staining were such that many of the cytologic features peculiar to osteoblasts could not be observed. The cells in the least differentiated areas had large nuclei; nucleoli were present, and the cytoplasm had distinct basophilic tendencies. An occasional mitotic figure could be seen, but cell processes were not observable (fig. 8 *A* and *B*).

The evolution of the tumor in the cellular areas was associated with the appearance of small aggregations of intercellular material between these cells, and the arrangement of the cells about the intercellular material in much the same way that young osteoblasts arrange themselves about new-formed osteoid trabeculae. The intercellular material stained red with eosin, pink with the van Gieson stain and blue with Mallory's aniline blue stain. It developed between the osteoblasts, but it was not possible to say whether or not it was a secretion product of the osteoblasts, though the histologic appearances suggested such an origin. It was acellular and seemed to be amorphous when stained with eosin, but it was thought that its fibrillar nature might be demonstrated by silver stains or the modified Weigert fibrin stain. These showed that the intercellular material was composed of coarse, irregular and decussating fibers which stained like collagen. The fibers extended from the osteoid aggregations to between the osteoblasts (fig. 8 *C* and *D*).

The small aggregations or trabeculae of intercellular material surrounded by cells had the histologic appearance of osteoid tissue. Between the osteoid trabeculae there was little cellular tissue. Some of the cells that did not differentiate into osteoblasts underwent degeneration, while others fused into large multinuclear osteoclasts. Few blood channels were observed. In spite of the marked cellularity of the lesion, one was impressed by the homogeneity of the process, and by the complete absence of tumor giant cells.

After the osteoid material was formed it continued to increase in size. As a result, the lining osteoblasts became flatter, and the cells and vessels between the osteoid trabeculae became compressed. When the growth of the osteoid tissue reached large proportions, numerous areas of anemic necrosis appeared in it, due to a poor vascularization, and liquefaction often resulted. Osteoclasts appeared about the necrotic tumor as an expression of a foreign body reaction. On the other hand, large amounts of calcium were deposited in the necrotic osteoid tissue, so that it was calcified; finally it was ossified. The calcific material was first deposited in the necrotic osteoid tissue as dust, cells grew into the lacunae, and bone resulted (fig. 9).

1. Jaffe, H. L.: Methods for the Histologic Study of Normal and Diseased Bone, *Arch. Path.* 8:817 (Nov.) 1929. Cameron, G. R.: Staining of Calcium, *J. Path. & Bact.* 33:929, 1930.

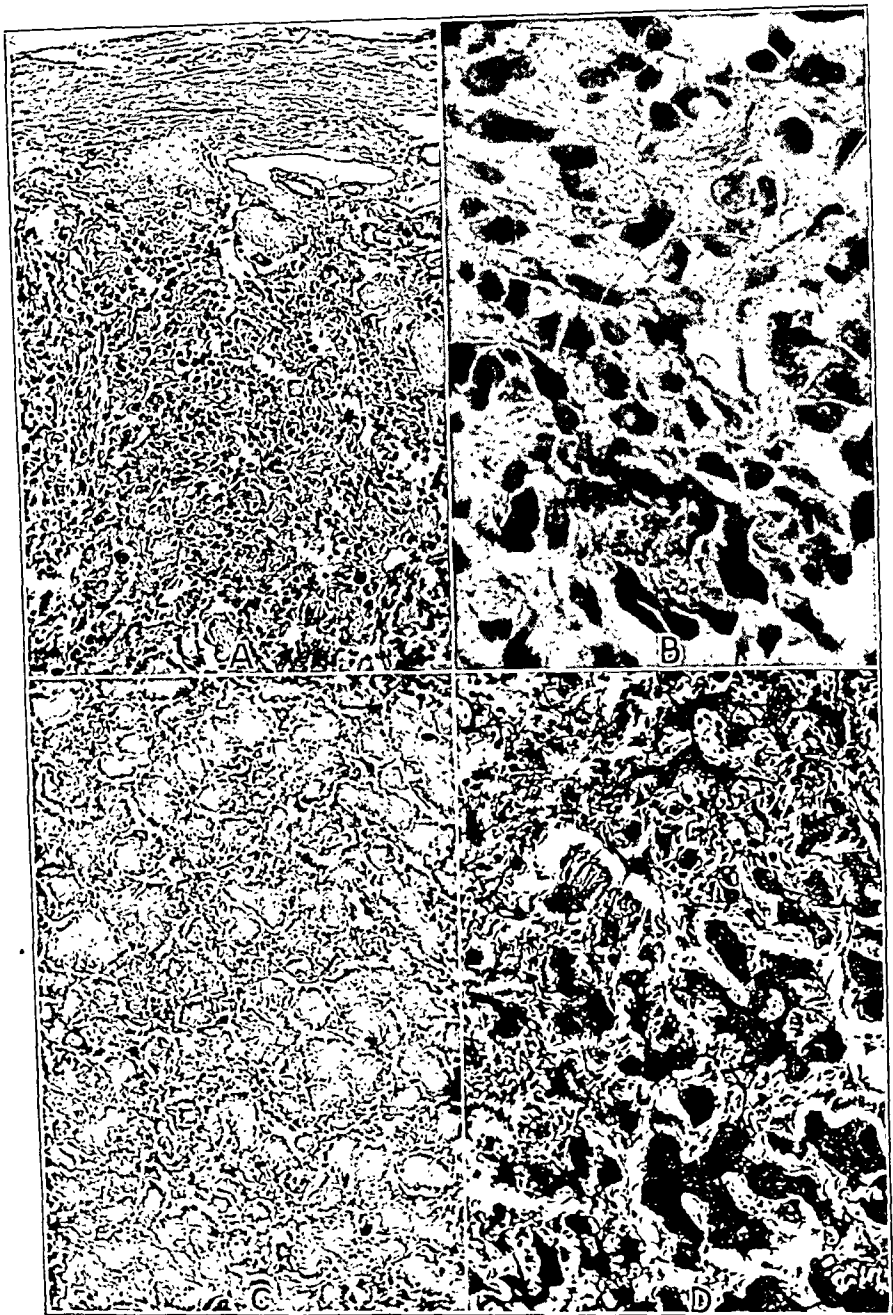


Fig. 8.—*A*, capsule of the tumor, immediately beneath which a thin trabecula of bone is seen. Beneath this, the cellular or least differentiated portion of the tumor is observed; $\times 135$. *B*, the same area under higher magnification; the intercellular material is more clearly evident; $\times 550$. *C*, further development of the tumor. The osteoid aggregations are lined by osteoblasts; $\times 60$. *D*, slide showing the fibrillar nature of the intercellular material; $\times 150$.

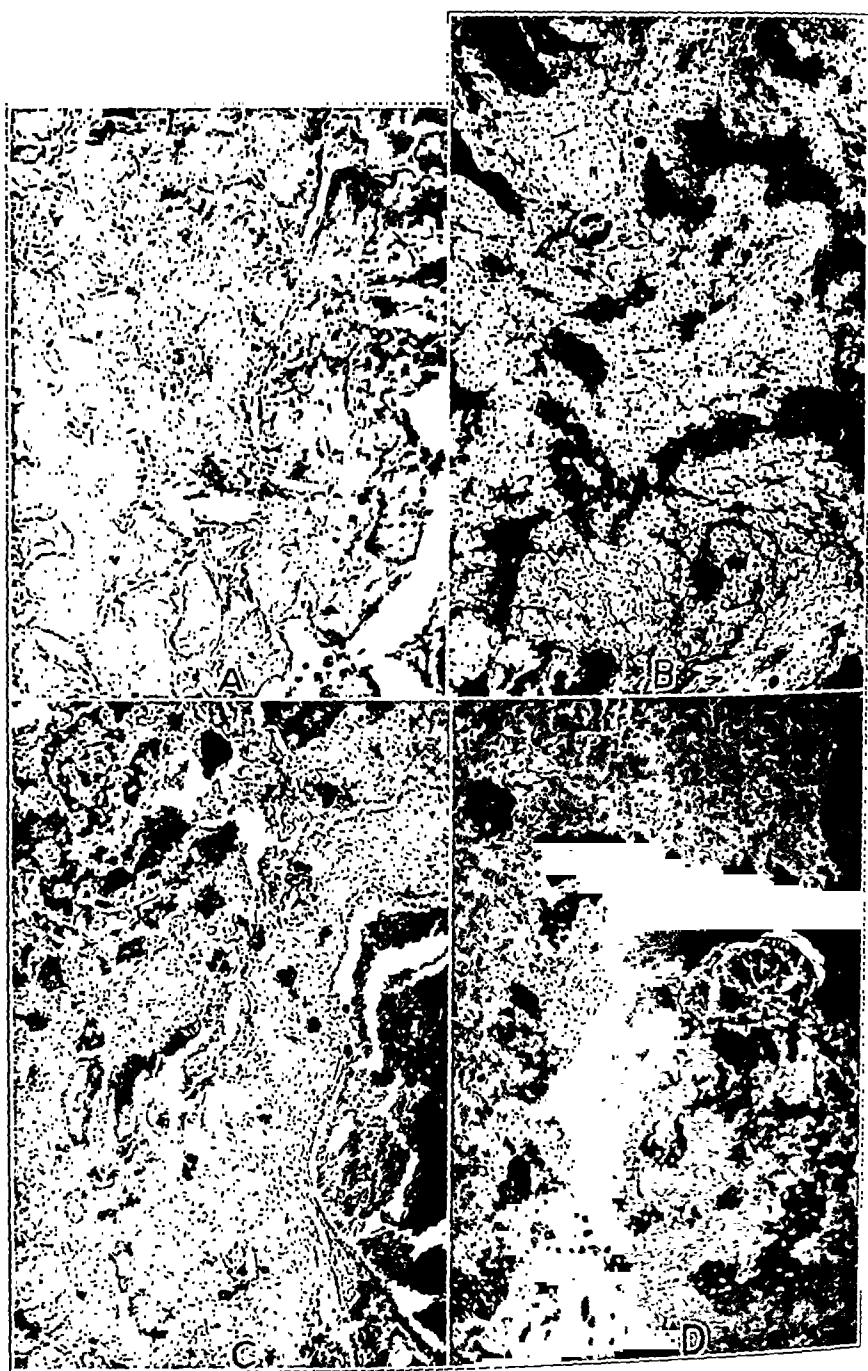


Fig. 9.—*A*, photomicrograph showing further growth of the intercellular osteoid material; the lining cells are flattened; $\times 120$. *B*, anemic necrosis and calcification of the osteoid tissue; $\times 120$. *C*, extensive calcification of the osteoid tissue and revascularization. Cells are reappearing and occupy lacunae; $\times 75$. *D*, ossification of the calcified osteoid tissue, with the formation of adult lamellar bone; $\times 75$.

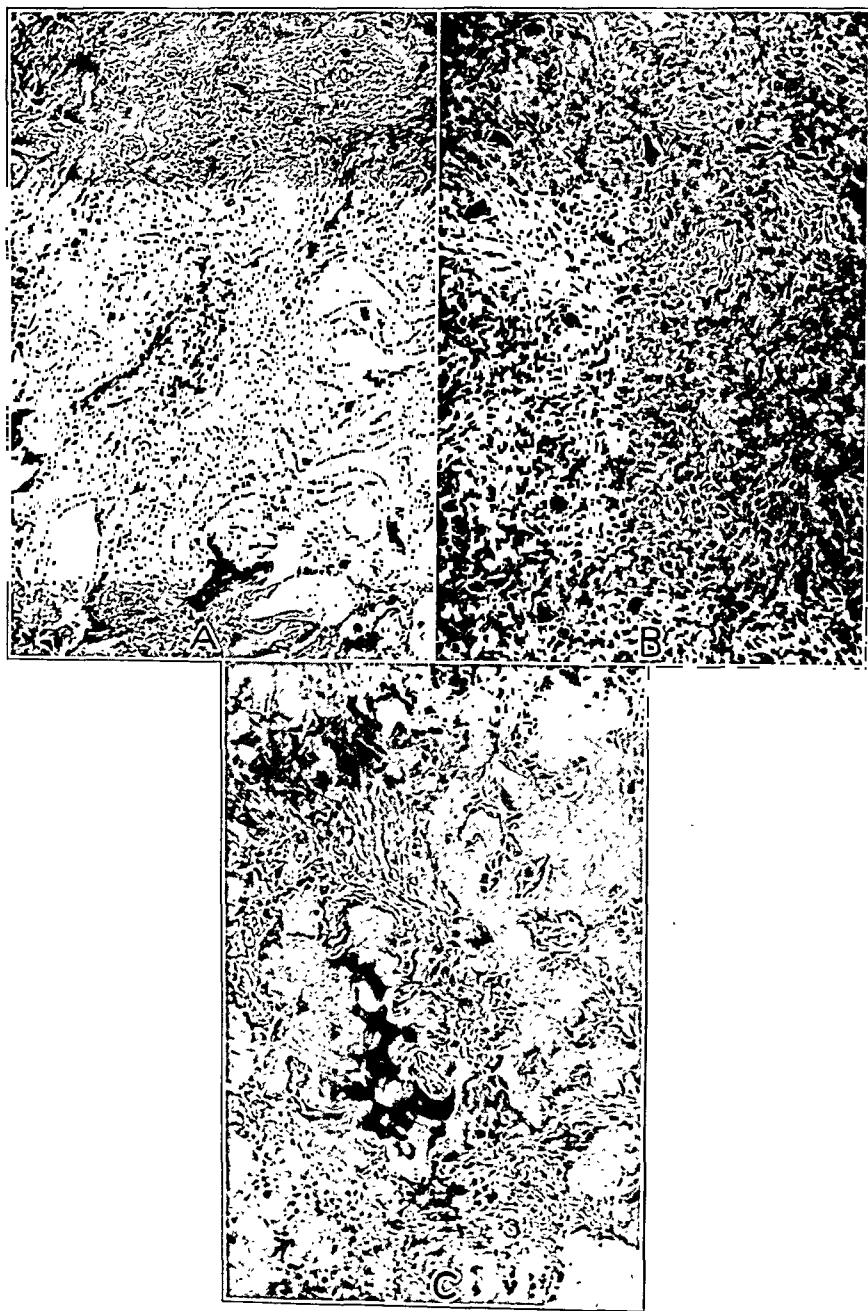


Fig. 10.—*A*, fiber-bone, the result of metaplastic ossification of spindle connective tissue. This appeared in numerous portions of the tumor; $\times 75$. *B*, a cellular area in section from the original biopsy; $\times 115$. *C*, intercellular osteoid material and calcified osteoid in section from the original biopsy; $\times 115$.

Furthermore, in and about the areas of necrosis, young spindle connective tissue appeared. Calcification of this connective tissue also occurred and trabeculae of fiber-bone were produced, the result of the direct ossification of this connective tissue. The trabeculae of ossified connective tissue were lined with osteoblasts. Considerable amounts of loose, fatty connective tissue could be observed between the formed trabeculae. Large vascular spaces and cysts were observed in this connective tissue. Osteoclasts in Howship's lacunae could be observed on some trabeculae. Transformation of the coarse-fibered bone into fine-fibered lamellar bone was also observed (fig. 10A).

The capsule of the tumor was fibrous tissue, of the nature of periosteum. Between the outermost zones of osteoid tissue and the capsule there was a thin layer of coarse-fibered bone.

In none of the numerous sections studied was there any evidence of encapsulated cartilage cells, cartilage matrix or mature cartilage tissue. We believe that this is of considerable significance, as the appearance of cartilage or cartilage cells in osteogenic sarcoma is an indication of the low order of differentiation of the cells from which the tumor arises. It is therefore evidence of greater malignant potentialities.

The histologic appearance of the sections prepared from the tissue removed in March, 1927, indicated that during a period of almost three years there had been no change in the morphologic nature of the tumor. The biopsy specimens showed a cellular osteoblastic tissue with a large amount of intercellular osteoid material. These sections were, however, more cellular than those prepared from the tumor (fig. 10B and C).

Sections of the tumor were submitted to a number of other pathologists, who declared the lesion to be a highly malignant osteogenic sarcoma. However, we suspected from the beginning that the usual bad prognosis of osteogenic sarcoma would be modified in this case because of the absence of cellular polymorphism and the presence of abundant osteoid tissue.

COMMENT

We are dealing with an osteoblastic tumor that possessed a great capacity to produce osteoid tissue as its characteristic feature. The locally destructive nature of the tumor is evidenced by the fact that nothing more than the articular surface of the head of the metacarpal bone remained. But, in spite of its rapid enlargement during the six months preceding its removal, the tumor remained confined within the periosteum. In the course of its histogenesis the formation of trabeculae of normal coarse-fibered bone as a result of calcification of connective tissue also occurred. This bone eventually underwent creeping replacement. The osteoid nature of the tumor was indicated by the fact that the intercellular material contained coarse, irregular fibrils but no calcium. Calcium, however, could be demonstrated in the necrotic osteoid tissue and in the trabeculae of the newly formed coarse-fibered bone.

Difficulties arise in classifying this tumor. It seems that to designate it as an osteogenic sarcoma, without further qualifications indi-

cating that it differs morphologically and clinically from the usual osteogenic sarcoma, is to miss the opportunity of appreciating that various types of bone-forming tumors exist. If it is classified as an osteogenic sarcoma, its unusual capacity to produce great amounts of osteoid tissue is truly striking, and must be taken into consideration. Furthermore, the fact that it had grown slowly and had not metastasized in nearly three years, or recurred a year and a half after local extirpation, speaks for its being a peculiar tumor. That malignant tumors show differences in growth and prognosis depending on the bone in which they arise is definitely known. The location of this tumor in the metacarpal bone may be the reason for its slow growth, and possibly also for its peculiar histologic nature. The rate of metabolic exchange is normally slower in the short than in the long tubular bones, and a metabolic factor may be the reason for the slow growth of this tumor.²

Virchow³ designated as "osteoid chondroma" an osteoid tissue-forming tumor that grew to great size but gave a better prognosis than osteosarcoma. He indicated that the "osteoid chondroma" was not related to the cartilage tumors of the chondroma type, but that it arose from cells capable of forming osteoid tissue. The confusing designation is due to the fact that in Virchow's time osteoid tissue was called "knochenknorpel." Though recognizing the characteristic nature of this type of tumor, he knew that "osteoid chondromas" might become malignant and change into osteosarcomas. He stated that these tumors may at one stage be soft and be cut with a knife, as they contain little or no calcium, but that when deposition of calcium does occur, this may be so considerable that the tumor can be cut only with a saw. The same view was held by Volkmann,⁴ who described an "osteoid chondroma" in von Pitha and Billroth's textbook of surgery, and indicated that these tumors were different from osteosarcoma. Like Virchow, he stated that the "osteoid chondromas," though giving the best prognosis, may undergo transition to enchondroma and osteosarcoma. Ribbert,⁵ however, classed the "osteoid chondromas" of Virchow with osteosarcomas.

2. Jaffe, H. I.; Bodansky, A., and Blair, J. E.: Rate of Decalcification and the Sites of Bone Lesions in Experimental Hyperparathyroidism, *Proc. Soc. Exper. Biol. & Med.* **28**:793, 1931; The Sites of Decalcification and of Bone Lesions in Experimental Hyperparathyroidism, *Arch. Path.* **12**:715 (Nov.) 1931.

3. Virchow, R.: *Die krankhaften Geschwülste*, Berlin, A. Hirschwald, 1863, vol. 1, p. 527.

4. Volkmann, R., in von Pitha and Billroth: *Handbuch der allgemeinen und speziellen Chirurgie*, Stuttgart, Ferdinand Enke, 1882, vol. 11, p. 462.

5. Ribbert, H.: *Geschwülstlehre*, ed. 2, Bonn, F. Cohen, 1914, p. 274.

Recently, Bergstrand⁶ reported two tumors that may be more closely related to the one being described. One of the patients was a girl, 16 years of age, with swelling and tenderness of the right foot of two months' duration. The metatarsal bone lesion was observed for thirteen months, and although it showed no enlargement, it became more painful. The entire diaphysis of the metatarsal bone was resected, and the patient made a complete recovery. The second patient was a boy, 18 years of age. For two years there had been increasing thickness of the middle finger. Roentgen examination showed a destructive lesion in the distal half of the diaphysis. The phalanx was removed, and there was no recurrence of the lesion after three years. Pathologic examination showed a disease focus situated in the proximal portion of the diaphysis of the metatarsal bone and in the distal portion of the diaphysis of the phalanx. The centers of the foci, which were the size of a pea, consisted of an amorphous collagenous material. The structureless mass was surrounded at the periphery by a relatively wide zone of richly vascular tissue which was traversed by newly formed bony trabeculae. From this peripheral zone numerous thin-walled vessels entered the homogeneous mass. The center of the mass was nearly free from vessels. Between the vessels and the amorphous material were large protoplasm-rich cells containing vesicular nuclei. Bergstrand believed that these were probably osteoblasts or closely related cells. The cell-poor amorphous material became continuous at the periphery with the trabeculae of bone. Here osteoclasts and Howship's lacunae were observed. The newly formed bony trabeculae were continuous with the preformed lamellar bone. In the preformed compact bone the vessel canals were enlarged and filled with loose fibrous connective tissue.

Bergstrand was at a loss to classify these lesions. He conceived them as having arisen through a local disturbance in bone formation, tracing this disturbance back to embryonal life. He believed that the homogeneous intercellular material most closely resembled the intercellular material of cartilage, and that it had resulted from a regressive change in embryonal cartilage. He was of the opinion that the lesions would have regressed spontaneously, the center of the focus being transformed into bone, had they not been operated on. We are inclined to think that the lesion described by Bergstrand is basically of the same nature as the one described here. He had two slowly progressing tumors capable of producing osteoid tissue. We believe that osteoid tumors exist; they resemble the "osteoid chondroma" of Virchow; they grow slowly, but may eventually grow rapidly; finally, if not adequately

6. Bergstrand, H.: Ueber eine eigenartige, wahrscheinlich bisher nicht beschriebene osteoblastische Krankheit in den langen Knochen der Hand und des Fusses, *Acta radiol.* **11**:597, 1930.

treated, they may take on rapid growth, and may even become malignant, developing all the features of an osteogenic sarcoma.

The difficulty in arriving at conclusions concerning the nature and prognosis of malignant tumors of the metacarpal bones is illustrated when the literature is searched for such tumors. Handl⁷ described two cases in 1906. One was a spindle cell sarcoma of the second metacarpal, occurring in a man 23 years of age. There was a history of a progressive swelling of the hand for about eighteen months, with encroachment, during the last three months, of the mass on the palm. The tumor was excised, but no follow-up history was given. The other case was that of a 19 year old boy who appeared with a tumor of the right hand, the size of a man's head. The phalanges of the thumb and the first and second metacarpal bones were completely involved, while the phalanges of the index finger and the bones of the radial portion of the wrist were only partially involved. No metastases were observed. The diagnosis arrived at from the amputated specimen was small round cell sarcoma with alveolar arrangement. No follow-up history was given, and some doubts may be entertained as to whether the lesion really was a primary malignant tumor of the metacarpal bones. It may have been a primary tumor of the soft tissue of the hand, secondarily invading the bones. The case reported by Bufalini⁸ was definitely one of metacarpal tumor. It arose from the third metacarpal bone, and was diagnosed as a spindle cell sarcoma with a small intercellular matrix. The patient, a boy 18 years of age, had the tumor for seven years. It enlarged the palmar and dorsal aspects of the hand to the size of an orange. The report of this case appeared shortly after the hand was amputated, and no follow-up history, photomicrographs or illustrations accompanied the report.

The osteogenic sarcoma group of tumors has probably most benefited by the recent classification of bone tumors by the American College of Surgeons. Previously these were given involved names, depending on the various modifications of bone-forming mesenchymal tissue seen in the section. As the histologic character of this tumor varies considerably in the different parts of the tumor examined, it is obvious that certain histologic criteria for the establishment of a diagnosis of osteogenic sarcoma had to be formulated. Histologic examination of our specimen showed that some of the criteria for a diagnosis of osteogenic sarcoma were fulfilled; there were, however, histologic

7. Handl, A.: Ueber ein grosses Sarkom der rechten Hand, Inaug. Diss., Erlangen, 1906; New York Academy of Medicine reprint no. 34353.

8. Bufalini, M.: Contributo allo studio anatomo-patologico e clinico dei sarcomi della mano e alla protesi cinematica a motore alternante dell'avambraccio, Arch. ital. di chir. 4:189, 1921.

features about the specimen that made it appear doubtful that we were dealing with a truly malignant osteogenic sarcoma. The clinical course of the case seems to bear this out.

SUMMARY AND CONCLUSION

We described an osteoid tissue-forming tumor of a metacarpal that began in a girl 12 years old. At first the tumor grew slowly. A biopsy was performed, the histologic sections showing osteoid tissue and numerous osteoblasts. The growth was slow for about the next two years, when it became very rapid. After growing rapidly for about six months, an encapsulated mass measuring 10 by 6.5 by 6 cm. was removed from the hand; section showed almost complete destruction of the metacarpal bone. The peculiar feature of this osteoblastic tumor was its capacity to produce large amounts of osteoid tissue, much of which was free from calcium. The tumor had some features common to osteogenic sarcoma, but showed a complete absence of cartilage or cartilaginous elements in numerous sections. It was especially characterized by homogeneity of the histologic picture, a lack of polymorphism of the cells and an absence of tumor giant cells.

There has been no recurrence one and a half years after extirpation.⁹ The patient has gained 25 pounds in weight, and has remained free from metastases for over four years after the original biopsy in March, 1927. We believe that the case demonstrates an instance of so-called "osteoid chondroma" of Virchow, which is an osteoid tissue-producing tumor, the prognosis of which is better than that of osteogenic sarcoma. It is our belief that had extirpation of the metacarpal bone been delayed much longer, the tumor probably would have undergone biologic transformation and developed the malignant capacities of true osteogenic sarcoma.

9. It is now (at the correction of the proof) two years since the tumor was extirpated, and the patient is in excellent health.

THE ACTIVITY OF ISOLATED INTESTINAL SEGMENTS *

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In the course of studies¹ dealing with the physiology of the discharge of bile into the intestine, it was noted that a segment of duodenum which was completely isolated from the remainder of the gastrointestinal tract increased in activity following oral administration of food, although food or gastric secretion did not come in contact with it. Increase of duodenal secretion and vascularity of the segment were also noted. Because there was no mechanical distention or direct stimulation of this segment by food or gas, the increased activity must have arisen from a nervous or circulatory stimulus. To investigate these observations further, studies were made of the activity of various segments of small bowel, isolated from the remainder of the intestinal tract and sutured to the abdominal wall. These segments soon recovered a healthy appearance and gradually resumed activity. Such preparations permitted direct observations on the activity of these segments in intact animals over long periods of time and under various conditions. Observations were made only on isolated segments of intestine and were limited to their activity before and after the animals had been fed. Later, the segments were completely denervated and the effects noted. Electrograms were also made and an interpretation of them suggested.

METHOD

The object of the surgical procedures (fig. 1) was to isolate segments of bowel from various portions of the small intestine and to bring them to the surface of the abdomen, where they could be studied by direct observation (fig. 2). The abdomen was opened under ether anesthesia and aseptic technic by an incision in the median line, of the same length as the contemplated segment of bowel, usually about 10 cm. The desired portion of intestine was identified and a segment found which was supplied with one large artery and its accompanying vein. The intestine was then sectioned at each end of the segment, and the mesentery split down to the root. The remainder of the intestine was reunited by end-to-end anastomosis. The isolated segment was brought out of the wound, and the muscle and fascial layers of the abdominal wall were closed beneath it by two or three interrupted linen sutures.

* Submitted for publication, July 13, 1931.

* Work done in the Division of Experimental Surgery and Pathology while a Fellow in Surgery, the Mayo Foundation, Rochester, Minn.

1. Puestow, C. B.: Discharge of Bile Into the Duodenum: An Experimental Study, *Arch. Surg.* **23**:1013 (Dec.) 1931.

Care had to be exercised to avoid strangulation of the mesenteric vessels. It was necessary to be sure that the ends of the segment were identified; usually the oral end of the bowel was placed in the cephalic end of the incision. The intestine was sutured to the skin and subcutaneous tissues by a continuous suture of catgut. This was placed close to the mesenteric attachment, so that most of the bowel was exposed. The isolated bowel soon underwent a severe inflammatory reaction, from

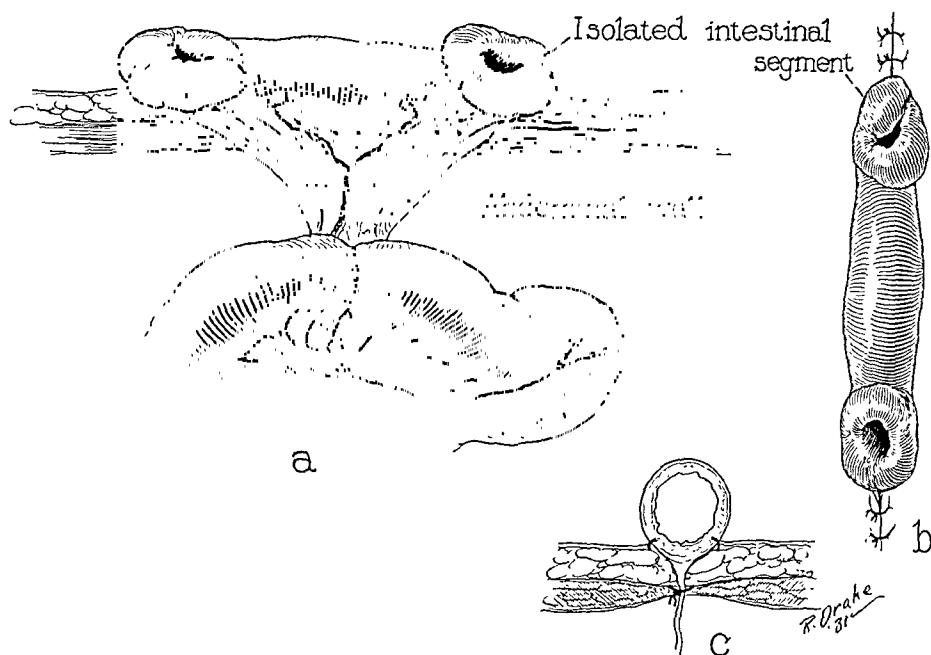


Fig. 1.—Operative procedures for isolation of an intestinal segment on the abdominal wall: *a*, lateral view; the broken line across the mesentery indicates where it and its enclosed structures eventually will be severed; *b*, view from without, with line of sight at right angles to the surface of the abdomen; *c*, view along longitudinal axis of isolated segment.



Fig. 2.—Isolated segment of ileum.

which it completely recovered in from ten to sixteen days. By this time it had resumed muscular and secretory activity.

In an effort to denervate the segment, the abdomen was opened by a rectus incision and all structures of the mesentery to the isolated bowel were sectioned, except the artery and the vein. The adventitial coats of these vessels were carefully dissected off to divide any nerve fibers accompanying them. Thus the blood vessels were the only original connections remaining between the isolated bowel and the

rest of the animal. However, because of the possibility of nerve fibers existing in the walls of the blood vessels, the abdomen was again opened, and the vessels were divided. This severed all original connections between the loop of bowel and the body, and established complete isolation of the segment from any direct influence of the central nervous system. Sufficient collateral circulation from the skin and subcutaneous tissue had become established to maintain the intestinal segment in an apparently healthy condition. To eliminate the effects of the sight, smell and taste of food, in one animal a gastric fistula was established which permitted feeding without these factors coming into play.

Direct observations were made of the isolated segments in various stages of fasting and digestion, before and after denervation. Several methods of recording the activity of the bowel were attempted. Balloons were placed in the lumen and attached to a recording tambour. This method was unsatisfactory, because the distended balloon stimulated the intestine to constant maximal contractions uninfluenced by feeding or fasting. Motion pictures were taken and gave fairly satisfactory records of the visible activity.

Electrograms were obtained by placing fine silver wire electrodes, coated electrolytically with silver chloride, 1 cm. apart on the long axis of the isolated intestinal segment. The oral electrode was connected with the right arm lead, and the caudad electrode was connected with the left leg lead of the electrocardiograph. The potential thus developed was measured and photographed in the usual way, and a fairly definite type of curve was obtained. The mechanical contact of the electrodes with the bowel did not seem to alter the activities of the latter in any way. Records were taken when the segments were visibly quiet and when they were visibly active, in fasting and nonfasting states, before and after denervation. The effects of peritonitis and of ether anesthesia were also noted.

RESULTS

Direct Observations.—In a series of dogs in which isolated segments of duodenum were transplanted onto the abdominal wall and opened longitudinally opposite the mesenteric attachment so that the mucosa was exposed, several factors relative to intestinal activity were noted. In the fasting state, there was usually very little muscular activity. Immediately after feeding there was either no change or an increase of activity lasting from one to two minutes. From fifteen to thirty minutes after ingestion of food, activity of the segment gradually increased, reaching a maximal activity in from a half to one hour. This degree of activity persisted for half an hour or longer, and then slowly diminished. Associated with this intensified muscular activity, there was an increase in duodenal secretion and greater hyperemia of the segment.

Observations on isolated segments of jejunum disclosed several interesting and rather constant features. In the fasting state, the bowel often appeared inactive and relaxed for periods of time varying from a few minutes to twenty or thirty minutes. At other times, it contracted regularly, but usually not strongly. When contractions were present, their rate was constant. In most animals there were cycles of activity. The contractions would begin feebly, would steadily increase to maximal

strength and then would diminish until they were no longer visible to the naked eye, and the bowel would appear inactive for from one to two minutes, when another active phase would begin. Such cycles were very regular, and usually lasted from four to six minutes. Feeding usually was followed in from twenty to forty minutes by greater muscular and secretory activity and increased hyperemia. The response was usually more delayed than it was in the duodenum. The increased muscular activity was manifested by stronger and more regular contractions, the rate remaining the same. In some animals the cycles of activity were not apparent after feeding; in others they persisted, but the inactive phase was relatively shorter, and during the active phase contractions were stronger. The muscular tonus of the segment was also increased. Increased activity following feeding was noted in most animals studied. In a few, in which increase was not definite, the jejunal segment was very active in the fasting state and remained so after feeding. To determine whether the taste, sight or smell of food initiated these responses, an animal was prepared with a gastric fistula through which it could be fed. When food was introduced into the stomach by this route, the response of the isolated segment of jejunum corresponded to those following oral feeding.

Isolated segments of ileum likewise had periods of quiet and of activity in the fasting state. However, a longer period of fasting seemed necessary to promote relaxation and diminished activity of the isolated segment of ileum than of the isolated segment of jejunum. The rate of contraction was slower and the cycles of contraction were less definite. Food seemed to stimulate increase of activity, but this response often was not apparent for one or more hours after feeding and was usually not marked. In general, it seemed that the various segments were most active when food was in the portion of the bowel from which the segments had been removed.

Observations were made after division of all extrinsic nerves to the various segments. The phenomena were not constant. Sometimes in the fasting state the segment would be inactive and relaxed for long periods of time; again it would contract regularly at maximal strength. The rate of contraction, however, was always constant for a given segment, and corresponded to the rate of that segment before denervation. Feeding likewise was followed by varying degrees of activity, but definite changes in activity could not be established as attributable to the ingestion of food. The hyperemia and increased secretion noted after feeding, before denervation, did not seem as definite after section of the nerves. Whether the animal fasted or was fed, the intestinal segments seemed to be least active when the animal was first placed on the table, and the strength and number of contractions seemed to increase slowly. The average amount of muscular activity under all

conditions was greater after than before denervation. Although evidence of cycles of contraction were found in a few cases, they were not as definite as when the nerves were intact.

ELECTROGRAMS

Electrograms were made without apparently disturbing the activity of the intestinal segments. Very definite complexes of altered electrical

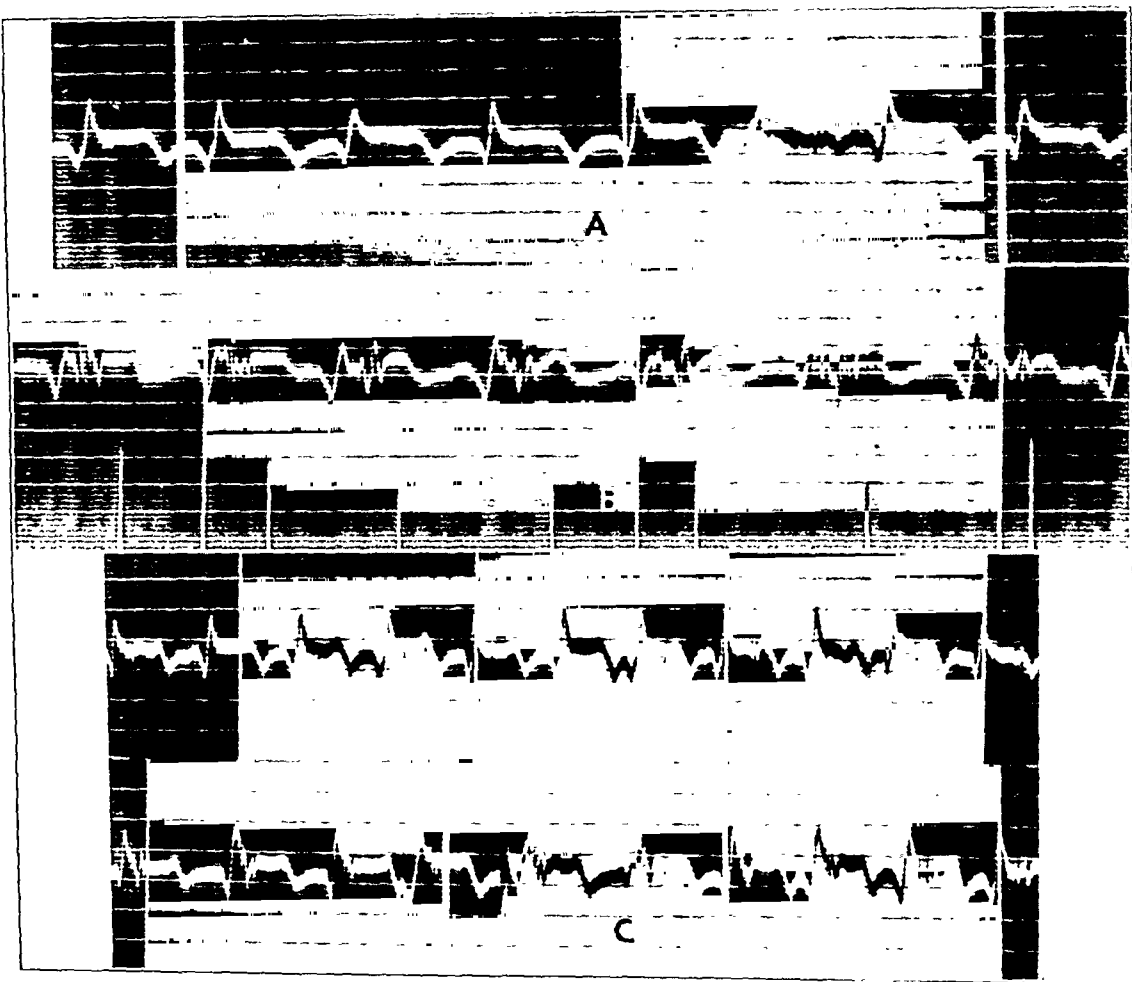


Fig. 3.—*A*, electrogram made when there was no visible contraction. *B*, electrogram made during visible activity. Signals indicate onset of each visible contraction. *C*, visible contractions were absent during the recording of the upper electrogram and were present during the recording of the lower one. All electrograms are of isolated jejunal segments. All time intervals, fifteen seconds.

potential could always be obtained in the healthy segment of intestine, whether or not visible activity was present (fig. 3). When contractions were visible, they always corresponded in time to the same phase of the complex recorded. More variation in this phase was seen when the

bowel was active than when it was quiet. The rate of intestinal contraction, when visible, always corresponded with the rate recorded in the electrograms. It was almost constantly uniform for each individual segment, whether the animal was in the fasting or in the nonfasting

TABLE 1.—*Electrographic Rates in Complexes per Minute Before and After Feeding*

Dog	Situation of Segment	Date	Non-fast-ing	Fast-ing	Hours After Feeding					
					0.5	1	1.5	2	4	24
1	Jejunum, 60 cm. below ligament of Treitz	May 13	10.6	10.4
		May 16	11.0	10.5	10.8	10.5
		May 30	10.4	10.0	10.0	10.0
		June 4	11.2	11.2	11.2
		June 6	11.0	11.0	11.0	11.0	11.0
		June 13	11.3
		June 21	12.0	12.0
2	Jejunum, 10 cm. below ligament of Treitz	May 30	11.3	10.4	10.0	10.0	10.0
		June 6	11.0	10.5	10.0
		June 13	9.0	(24 hours after denervation)					
		July 27	11.0	10.5	10.5	10.5	10.7
		July 28	11.0
		August 4	11.2
3	Jejunum, 12 cm. below ligament of Treitz	May 30	12.0	12.0	12.0	12.0
		June 4	13.0	12.0	12.7
		June 13	12.0	(24 hours after denervation)					
		June 25	12.0
4	Ileum, 50 cm. above ileocecal juncture	May 15	9.7	9.7
		May 17	9.5	9.5	9.5	9.5
		May 19	9.5
		May 27	9.2	9.2	9.0	9.0	9.0	9.5
		May 30	9.0	9.2	9.0	9.0
		June 6	9.0	9.0	9.0	9.0	9.0
		June 21	9.4	9.4
		June 25	9.0

TABLE 2.—*Electrographic Rates According to Situation of Segment*

Dog	Situation of Segment	Rate in Complexes per Minute		
		Average	Maximal	Minimal
5	Duodenum at ampulla of Vater.....	18.4
6	Duodenum at ampulla of Vater.....	18.0
7	Duodenum at ampulla of Vater.....	17.0
8	Duodenum at ampulla of Vater.....	15.5
9	Duodenum below ampulla of Vater.....	14.0
2	Jejunum, 10 cm. below ligament of Treitz.....	10.6	11.3	10.0
3	Jejunum, 12 cm. below ligament of Treitz.....	12.2	13.0	12.0
10	Jejunum, 40 cm. below ligament of Treitz.....	13.0	13.2	12.7
1	Jejunum, 60 cm. below ligament of Treitz.....	10.8	12.0	10.0
4	Ileum, 50 cm. above ileocecal juncture.....	9.2	9.7	9.0
11	Ileum, 50 cm. above ileocecal juncture.....	9.3

state. In some instances feeding seemed to slow the rate very slightly, but this was not constant (table 1). Similar records were obtained after denervation, and the rate was not altered. The rate of complexes as recorded on the electrograms varied with the portion of the intestine from which the segment had been isolated. It was most rapid in the duodenum, less rapid in the jejunum and least rapid in the ileum (table 2).

To ascertain that the electrical responses were not due to activity of the muscularis mucosae, the latter with the mucosa was stripped off from an isolated segment of the bowel. Records obtained after this procedure were similar to those made before it. Electrograms were made with the segment in various stages of inflammation. As the disease became more advanced, the electrical responses grew weaker, and slightly less rapid, until they finally disappeared. When the segment began to recover from the inflammation, the responses returned and gradually increased to normal strength and rate. Throughout this time there was no visible activity. Records were made with several animals intact, and then with them under ether anesthesia. It was found that the rate of responses diminished in proportion to the depth of anesthesia and returned to the normal rate when the animals had recovered from the narcosis.

COMMENT

Direct observation of isolated segments of intestine exposed on the abdominal wall showed them to have a certain degree and nature of activity when the animal was in the fasting state. After feeding there was an increase of muscular and secretory activity and hyperemia of the segment. These changes were greatest in the duodenal segments, less marked in the jejunal portions of bowel and least noticeable in the lower part of the ileum. The onset of response appeared earliest in the duodenum, and the latent period increased proportionately to the distance down the intestinal tract at which the segment was isolated. It seemed that greatest activity corresponded to the time during which food was in the portion of the bowel from which the segment had been removed. Food did not come in contact with these isolated segments, because there was no direct contact between them and the remainder of the intestinal tract. Therefore, the stimulation causing increased activity of these segments must have been transmitted through nervous or vascular routes. In an effort to determine the importance of the extrinsic nerve supply, all possible fibers going to the segment were severed. Following this, there was not the definite increase in muscular and secretory activity and in hyperemia after feeding that had been noted before denervation. Although general activity of the segments was greater, no definite influence exerted by food could be established. This suggested that extrinsic nervous control was a factor in the responses to feeding of the isolated segments of intestine, and that nerve fibers reaching the bowel by way of the mesentery seem to have an inhibitory and regulatory power. An animal fed through a gastric fistula responded in a manner similar to those fed orally. This indicated that the stimuli were not due only to the sight, taste or smell of food.

Electrograms of isolated intestinal segments demonstrate some definite and constant complexes that can be divided into four phases and

interpreted as follows (fig. 4): (a) A sharp negative and then a positive deviation occurs, which is considered to be due to the spread of excitation in the muscles. Whether this is of neurogenic or myogenic origin has not been determined. (b) A prolonged phase of positively altered electrical potential follows. Visible contractions of the isolated bowel always correspond in time to this positively altered phase and are signalized by the appearance of fine oscillations, which are seen chiefly in the early part of this phase, but which sometimes also occupy the latter portion of the preceding phase. The number and amplitude of these fine oscillations are fairly proportional to the degree of visible activity. When the intestine is not visibly active, this phase is uniformly

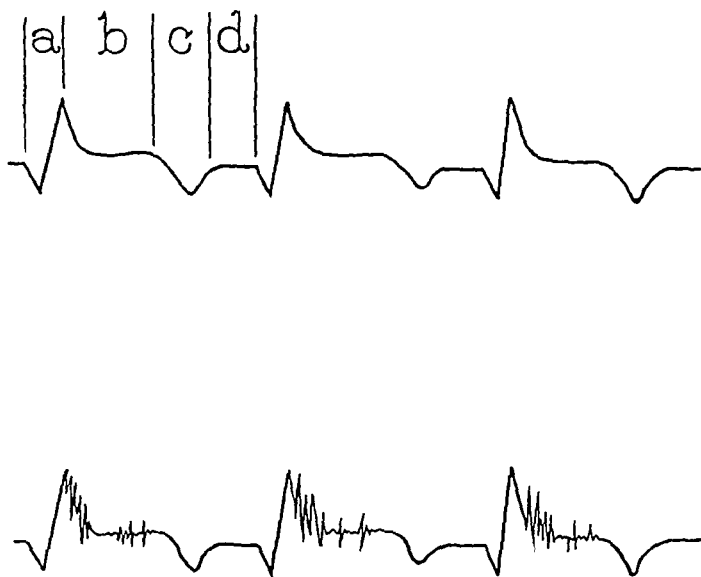


Fig. 4.—Interpretation of electrogram. Upper type obtained when there is no visible intestinal activity. Lower type obtained when there is visible activity of transplanted intestinal segment. Excitation phase is indicated by *a*, phase of muscular tension or activity by *b*, end of muscular activity by *c*, and iso-electric or resting phase by *d*.

level and is probably due to altered muscular tension not visible to the naked eye. (c) There is a final deflection that is similar to an inverted T wave of the electrocardiogram and probably represents the end of muscular activity. (d) A short iso-electric phase is seen. This probably corresponds to a resting phase before the next stimulus occurs.

The rate of these electrical complexes for a given segment was almost constantly uniform and regular in both fasting and nonfasting states of the animal. Denervation did not noticeably alter the electrograms either in the form or rate of the complexes. This suggests that these complexes are due to some intrinsic mechanism in the segment. It also suggests that a rhythmic activity is taking place in the intestine at all

times, and that ingestion of food only changes the intensity of the contractions and not the rate. The rate, as recorded by the electrogram, corresponded to the rate of visible contractions when they were present, and the same rate continued when no activity could be seen. It was greatest at the oral end of the intestine and diminished toward the terminal portion of the ileum. This gradation in rate is in conformity with the observations that Alvarez² has been making for a number of years on the intestinal gradient. In only two conditions studied were any marked changes in rate noted; these were inflammation of the isolated segment and deep ether anesthesia, in both of which the rate was moderately diminished. Alvarez and Mahoney,³ in 1924, obtained electro-enterograms of peristaltic rushes passing various points of the intact intestinal tract of rabbits. Their records were not interpreted, but some of them bear a certain degree of similarity to electrograms obtained in this study on isolated intestinal segments.

SUMMARY

Various segments of bowel were isolated from the intestinal tract and transplanted onto the abdomen. It was observed that feeding stimulated an increase of muscular and secretory activity and hyperemia of these segments. Because food did not come in contact with the segments, the stimulus must have been carried by nervous or vascular pathways. Following division of all extrinsic nerves to these intestinal transplants, the response to food could not be clearly demonstrated. This suggested that the increased activity after feeding was at least partially due to extrinsic nervous control.

Electrograms made of these various isolated segments of intestine revealed a characteristic curve of altered potential. They also showed a constant rate for a given segment under most conditions studied. The rate was most rapid in duodenal segments, less in jejunal segments and slowest in segments of the lower part of the ileum. Peritonitis and ether anesthesia were found to diminish this rate moderately.

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CONCRETIO CORDIS

II. CARDIOLYSIS FOR CONCRETIO CORDIS *

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The surgical problems involved in the treatment for concretio cordis are distinctly different from those involved in the treatment for mediastinopericarditis. In mediastinopericarditis, the main indication is relief from interference with the systolic contractions of the heart. Relief is most easily and efficiently obtained by resecting the bony and cartilaginous structures of the thoracic wall in the area overlying the heart, a procedure described by Brauer. In concretio cordis, the thickened pericardium contracts about the heart and prevents adequate filling of the cardiac chambers during diastole. In some cases there are adhesions between the thickened pericardium and the surrounding structures, while in others the pericardial walls are calcified or are so greatly thickened that the systolic contractions of the heart are seriously interfered with. In any case, the primary difficulty is with diastole, and relief can be expected only from a release of the heart by removal of the constricting membrane. Excision of this constricting membrane, or decortication of the heart, was first advocated by Delorme ¹ in 1898, but was not carried out until 1913 when Sauerbruch ² successfully performed the operation. Since that time, Rehn,³ Schmieden,⁴ Churchill ⁵ and others have reported cases of concretio cordis in which this method of treatment was used.

Before entering into a more detailed discussion of the surgical treatment of this condition, two instances will be described in which removal of the thickened pericardium was attempted. These two cases have been presented in more detail in paper I ^{5a} on this subject.

REPORT OF CASES

CASE 1.—The patient in this case was operated on on Feb. 15, 1930, after local injection of procaine hydrochloride and administration of nitrous oxide anesthesia.

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* From the Department of Surgery, Vanderbilt University School of Medicine.

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3. Rehn, L.: Pericardial Adhesions in Children, *Arch. f. Kinderh.* **68**:179, 1920.

4. Schmieden, V.: The Technique of Cardiolysis, *Surg., Gynec. & Obst.* **43**:89, 1926.

5. Churchill, E. D.: Decortication of the Heart (Delorme) for Adhesive Pericarditis, *Arch. Surg.* **19**:1457 (Dec.) 1929.

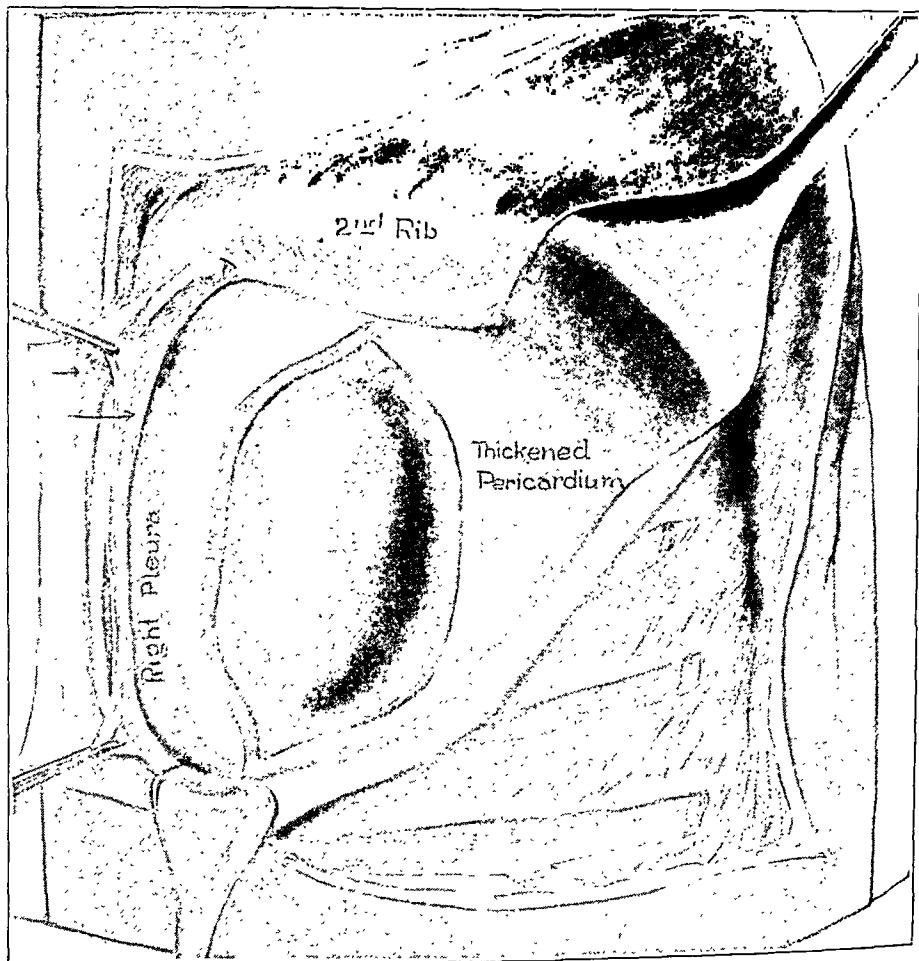
5a. Burwell, C. S., and Strayhorn, W. D.: Concretio Cordis: I. A Clinical Study, With Observations on the Venous Pressure and Cardiac Output, *Arch. Surg.* **24**:106 (Jan.) 1932.

A curved incision was made from the lower border of the second costal cartilage just to the left of the sternum, carried down along the left border of the sternum to the sixth costal cartilage, and then curved outward along the lower border of the sixth cartilage to approximately the left nipple line. The muscles were divided down to the ribs, and the skin muscle flap retracted laterally. The third, fourth, fifth and sixth cartilages, perichondrium and intercostal structures were removed. In removing the fifth cartilage, a small opening was made in the left pleura but this was closed by a plug of fat and did not cause any respiratory upset. The internal mammary artery was doubly ligated and divided. The left half of the sternum between the third and sixth cartilages was removed. The left pleura was dissected from the pericardium to the midportion of the left border of the heart. The pericardium was then incised in line with the left border of the sternum and separated for a distance of 4 cm. toward the left. The dissection was easily done with the finger. In separating the pericardium over the upper portion of the right ventricle, the line of cleavage led between the somewhat transverse muscle fibers because the fibrous bundles dipped in between them. Dissection at this point was being done blindly, so the separation of the muscle fibers was not noticed until the chamber of the right ventricle was entered. Little pressure was used during this dissection, and it was obvious that the wall of the ventricle was greatly thinned out at this point. When the ventricle was entered, there was a serious hemorrhage which was controlled with difficulty. The muscle fibers were so friable that it was decided that it would not be wise to attempt to close the opening by suturing the muscle. As only a small amount of pericardium had been dissected up, the hemorrhage was controlled by closing the opening in the pericardium. This apparently completely controlled the hemorrhage, but the patient had lost a large quantity of blood during the closure, and signs of severe shock developed. He was given 500 cc. of physiologic solution of sodium chloride intravenously, with distinct benefit. The wound was closed without drainage.

Three hours later, the condition of the patient again became alarming. A transfusion of 500 cc. of whole blood was given, following which there was improvement for several hours, but the blood pressure rose to only 75 systolic and 55 diastolic. Another transfusion was considered, but as it was feared that too great strain would be added to the already weakened heart, it was not done. About twelve hours after operation the patient's condition rapidly changed for the worse, and he died within a short time. The cause of death was not clear, but it was apparently due to shock and hemorrhage in a person with extremely low cardiac reserve.

CASE 2.—A young colored man was operated on on June 11, 1929. The operation was carried out under local injection of procaine hydrochloride and light nitrous oxide anesthesia. The incision was begun just below the inner end of the second costal cartilage and carried down to the sixth costal cartilage and then out to approximately the left nipple line. The skin muscle flap was dissected up and retracted laterally. The third, fourth and fifth cartilages and ends of the ribs as well as the anterior portion of the periosteum and perichondrium were resected. The left half of the sternum was removed by rongeur between the second and sixth cartilages. The left pleura was exposed and dissected laterally as far as the midportion of the left border of the heart. The right pleura was separated from the pericardium to the right border of the heart. It was densely adherent, and while it was being freed a small opening was obtained in the pleura, which was promptly closed with a catgut suture without any appreciable collapse of the right lung. The pericardium was then incised in a longitudinal

direction, but no pericardial cavity was found. The epicardium was incised, and a line of cleavage discovered. The thickened pericardium and well organized exudate over the epicardium were then removed from the anterior surface of the right side of the heart. The dissection was carried to the left slightly beyond the junction of the right and left ventricles. The line of cleavage was imperfect, making it necessary to do the major portion of the operation by sharp dissection. When an attempt was made to liberate the left ventricle, it was discovered to be so densely adherent and there were so many fibrous trabeculae extending down into the heart muscle that it was decided that further separation would be



The left pleura was stripped back and the pericardium exposed. It was 4.5 mm. thick and adherent throughout. When incised the heart promptly bulged through. The parietal pericardium over the anterior surface and right side of the heart was excised. The anterior (short arrow) and posterior layers of periosteum (long arrow) of the sternum were sutured together to prevent regeneration of the resected portion.

unwise, as it was feared that the wall of the heart would be injured. When the pericardium was first incised and separation started, there was a distinct bulging of the wall of the right ventricle through the opening (see illustration).

The anterior and posterior layers of periosteum of the sternum were sutured together to give a smooth surface and to prevent regeneration of the excised bone. The muscles, fascia and skin were closed without drainage.

The pericardium was composed of dense fibrous tissue 4.5 mm. thick. Microscopic examination revealed no evidence of active tuberculosis.

The patient's condition remained satisfactory throughout the operation, and the blood pressure was maintained at approximately 110 systolic and 80 diastolic for the next six days. A rather persistent hiccup developed which was relieved by the inhalation of carbon dioxide and oxygen.

On June 17, six days after operation, the patient complained of severe pain in the region of the heart, and the blood pressure fell. The heart sounds became muffled, and there was fulness in the precordial area, indicating a collection of fluid between the thoracic wall and the heart. One hundred and twenty cubic centimeters of bloody fluid was aspirated from beneath the skin-muscle flap; the fluid was negative on culture and on inoculation into guinea-pigs. Following the aspiration of this fluid, the blood pressure rose to 110 systolic and 80 diastolic, and the patient's general condition showed improvement. The precordial space was again aspirated on June 20, and 20 cc. of fluid was removed. On June 25, the left pleural cavity was aspirated, and 1,000 cc. of serosanguineous fluid was removed; 50 cc. of blood-tinged fluid was also aspirated from the precordial space. On June 26, 800 cc. of clear straw-colored fluid was removed from the right pleural cavity, and on June 29, 800 cc. of blood-tinged fluid was removed from the left pleural cavity.

The patient's condition steadily improved until the time of his discharge from the hospital on July 25, 1929. When he was seen on August 16, there was no fluid in the right pleural cavity and only a small amount in the left. The heart sounds were strong and clear. There was a small amount of fluid in the peritoneal cavity, and the liver was enlarged. On August 28, the fluid in the peritoneal cavity had almost disappeared, but the liver remained approximately the same size.

On September 26, the patient returned complaining of pain in the left side of the chest. There were again signs of a large collection of fluid in the left pleural cavity. There was no demonstrable fluid in the peritoneal cavity, and the liver had apparently decreased to almost normal size. Fifteen hundred cubic centimeters of straw-colored fluid was aspirated from the left pleural cavity on September 30, and 1,700 cc. on October 4. Cultures of the fluid and inoculations into guinea-pigs were negative. On October 29, there was only a small amount of fluid in the left pleural cavity, and none in the right. On November 27, there was no fluid in either pleural cavity. The liver was only slightly enlarged, but a moderate amount of fluid was present in the peritoneal cavity. There was no edema of the extremities, no shortness of breath and no pain in the chest.

The patient entered the hospital on Dec. 1, 1929, complaining of pain in a left inguinal hernia. He was operated on on December 4, and the peritoneum found to be studded with tubercles, but the wound healed well and the patient was discharged on Jan. 4, 1930.

He reentered the hospital on May 11, 1930, complaining of marked distention of the abdomen. A small incision was made just to the right of the midline, midway between the umbilicus and pubis, and about 6 liters of straw-colored fluid was removed; it rapidly reaccumulated, and 4 liters of fluid was removed by paracentesis on May 30. The patient was discharged on June 9, distinctly improved.

When last seen on July 2, 1930, there were no edema, no fluid in the pleural cavities, no shortness of breath, no enlargement of the liver and no symptoms referable to the circulatory system. There was much less fluid in the peritoneal cavity, and this was partially encysted on the left side.

in the more advanced cases where one would expect to find a marked atrophy of the cardiac muscle. However, it would be much more logical to carry the first stage a step further than that suggested by Cutler and excise at least a portion of the pericardium, preferably over the junction of the right and left ventricles, thus giving systolic relaxation and also a certain amount of diastolic relief without actually removing enough of the supporting wall to allow acute dilatation of the right side of the heart. This should improve the circulation and permit the weakened heart muscle to regain its tone before the more extensive decortication is attempted.

Technic of Excision of the Pericardium.—The actual removal of the thickened pericardium may be extremely difficult and occasionally impossible. The removal of the pericardium without removing the thickened epicardium would be much less difficult and as a rule less dangerous, but the epicardium is usually so greatly thickened that little benefit could be expected if this were left intact. It is therefore necessary to remove both the thickened pericardium and epicardium to permit a satisfactory diastole. In the long-standing cases the fibrous strands are apt to dip in between the cardiac muscle fibers and make the dissection difficult. Most authorities advise combined sharp and blunt dissection with removal of small fragments of pericardium as they are freed. It would seem less dangerous to use sharp dissection almost entirely, and it is especially important to keep the operative field under direct vision throughout the dissection. In one of the cases here reported this was not done, and there was a rupture of the wall of the right ventricle. In all probability this would not have occurred if the operative field had been fully visible at the time, as the separation of the muscle fibers would have been noticed.

It would seem advisable to leave the pericardium in place during the early portion of the dissection, so that if the chamber of the heart were entered the pericardium could be used to help close the opening and control the hemorrhage. This is important when the cardiac muscle is atrophic and friable, as sutures would almost certainly cut through.

Schmiedden, Cutler and others feel that it is important to remove the pericardium over the left ventricle first since they fear a dilatation of the weakened right ventricle if the support is removed from the anterior surface of the heart before the left ventricle is released. This seems a logical assumption, and yet in Churchill's case and in case 2 reported here the greater portion of the dissection was carried out over the right ventricle, and in neither case was there serious difficulty as a result of this.

RESULTS

Churchill tabulated the results in thirty-seven cases that he was able to collect from the literature. Five cases were interrupted. Of those

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COMMENT

Type of Incision.—Excision of the thickened pericardium can be carried out through a number of incisions. First, a long midsternal incision⁶ can be made which gives an excellent exposure to the right side of the heart but a less adequate exposure to the left side, and which has the obvious disadvantage that the rigid thoracic wall will be intact when the wound has healed. Schmieden advocated a transpleural approach to the left side of the heart by a long intercostal incision. This type of incision has two disadvantages: First, the open pneumothorax adds a considerable burden to the heart even though the operation is carried out under positive pressure anesthesia; second, when the wound heals there is no relaxation of the anterior thoracic wall over the pericardium. It has the advantage, however, of giving a much more direct exposure of the left ventricle, which Schmieden thinks is of great importance. The third type of incision is that used in the Brauer pericardiolysis. A curved incision is started at approximately the level of the lower border of the second costal cartilage and carried downward and then outward along the sixth or seventh costal cartilage. The incision is carried down to the ribs, and the skin muscle flap retracted laterally. The ribs, cartilages, periosteum and intercostal structures are excised. A portion of the left side of the sternum may be excised so as to give a more adequate approach to the right side of the heart. This incision gives an excellent exposure of the right side of the heart and a relatively satisfactory exposure of the left side. It has two advantages: First, it is not necessary to have an open pneumothorax during the operation; and second, the thoracic wall over the pericardium is permanently relaxed. This would seem to be of importance, because it is almost certain that extensive adhesions form between the structures of the thoracic wall and the anterior surface of the heart. If the wall of the chest remains rigid, the clinical picture may be converted into one simulating mediastinopericarditis. In other words, the diastolic difficulty may be largely relieved only to be replaced by an interference with systole.

Number of Stages.—Cutler⁷ advocated that the operation be divided into at least two or possibly three stages. He has suggested that the first stage consist of a Brauer pericardiolysis, and that at the second stage the thickened pericardium be removed from the surface of the left ventricle and also from the surface of the right ventricle if it is felt that the patient's condition will stand such an extensive procedure. It would seem advisable to divide the operation into two stages, especially

6. Lilienthal, Howard: Thoracic Surgery, Philadelphia, W. B. Saunders Company, 1925, vol. 1, p. 422.

7. Cutler, E. C.: Surgery of the Heart and Pericardium, in Nelson's Loose-Leaf Surgery, New York, T. Nelson & Son, 1927, vol. 4, p. 372.

in the more advanced cases where one would expect to find a marked atrophy of the cardiac muscle. However, it would be much more logical to carry the first stage a step further than that suggested by Cutler and excise at least a portion of the pericardium, preferably over the junction of the right and left ventricles, thus giving systolic relaxation and also a certain amount of diastolic relief without actually removing enough of the supporting wall to allow acute dilatation of the right side of the heart. This should improve the circulation and permit the weakened heart muscle to regain its tone before the more extensive decortication is attempted.

Technic of Excision of the Pericardium.—The actual removal of the thickened pericardium may be extremely difficult and occasionally impossible. The removal of the pericardium without removing the thickened epicardium would be much less difficult and as a rule less dangerous, but the epicardium is usually so greatly thickened that little benefit could be expected if this were left intact. It is therefore necessary to remove both the thickened pericardium and epicardium to permit a satisfactory diastole. In the long-standing cases the fibrous strands are apt to dip in between the cardiac muscle fibers and make the dissection difficult. Most authorities advise combined sharp and blunt dissection with removal of small fragments of pericardium as they are freed. It would seem less dangerous to use sharp dissection almost entirely, and it is especially important to keep the operative field under direct vision throughout the dissection. In one of the cases here reported this was not done, and there was a rupture of the wall of the right ventricle. In all probability this would not have occurred if the operative field had been fully visible at the time, as the separation of the muscle fibers would have been noticed.

It would seem advisable to leave the pericardium in place during the early portion of the dissection, so that if the chamber of the heart were entered the pericardium could be used to help close the opening and control the hemorrhage. This is important when the cardiac muscle is atrophic and friable, as sutures would almost certainly cut through.

Schmieden, Cutler and others feel that it is important to remove the pericardium over the left ventricle first since they fear a dilatation of the weakened right ventricle if the support is removed from the anterior surface of the heart before the left ventricle is released. This seems a logical assumption, and yet in Churchill's case and in case 2 reported here the greater portion of the dissection was carried out over the right ventricle, and in neither case was there serious difficulty as a result of this.

RESULTS

Churchill tabulated the results in thirty-seven cases that he was able to collect from the literature. Five cases were interrupted. Of those

completed, there was an operative mortality in seven cases, or 21.8 per cent, no improvement in two cases, or 6.2 per cent, transient improvement in four cases, or 12 per cent, and almost complete relief from symptoms in nineteen cases, or 59 per cent.

In case 1 the operation was interrupted because the chamber of the right ventricle was accidentally entered. The patient died twelve hours later from shock and hemorrhage. The patient in case 2 withstood the operation well, and at the time this article was written, fourteen months later, had no symptoms referable to the heart. He has a tuberculous peritonitis, especially dangerous in the colored race, from which he seems to be recovering.

CONCLUSION

Decortication of the heart is a formidable operation, but one which is distinctly indicated for the relief of concretio cordis, a disease which without surgical intervention is hopeless. The mortality rate is high and will of necessity continue to be so, but with improved operative technic one of the chief dangers, rupture of the heart, should be greatly diminished. If a satisfactory two-stage operation can be developed, the incidence of postoperative dilatation of the heart should be decreased.

SQUAMOUS CELL CARCINOMA OF THE KIDNEY

WITH COMPLETE INFARCTION OF THE KIDNEY AS A SEQUEL TO
CANCEROUS THROMBOSIS OF THE RENAL ARTERY *

JACOB RABINOVITCH, M.D.

ST. LOUIS

The case reported in this paper seems worthy of being placed on record for two reasons: first, because a fairly thorough review of the literature has failed to reveal a similar case of a malignant condition in which the renal artery was completely occluded by a cancerous thrombus, and, second, because total infarction of the kidney is a rarity.

REPORT OF A CASE

History.—A white woman, aged 64, a housewife, entered the Missouri Baptist Hospital, on Feb. 7, 1931, complaining of abdominal pains of five months' duration. At the onset of her present illness the pain was dull and achy, but during the last three weeks it had gradually become more intense and continuous, changing to a stabbing nature. It was not associated with any urinary disturbances, such as dysuria, polyuria or hematuria. Beyond pain, there was no other physical disturbance.

Examination.—Physical examination revealed the following positive findings: On the left side of the abdomen there was a localized area of tenderness, which was confined to the region of the left kidney. The left kidney could not be palpated, however. The cystoscope showed the vesical mucosa moderately congested but otherwise normal. Ureteral catheterization showed that the left kidney did not function. When 1 cc. of phenolsulphonphthalein was injected intravenously, no dye appeared from the left kidney in thirty minutes; the right kidney functioned normally. Cultures made of the catheterized urine obtained from the bladder and kidneys revealed no bacterial growth. Roentgenograms taken after the injection of sodium iodide by the ureteral catheters disclosed a block above the left catheter. No pelvic shadow was obtained on the left side, while the right kidney appeared normal.

Urinalysis was essentially negative. Analysis of the blood showed: total non-protein nitrogen, 39.4 mg. per hundred cubic centimeters; erythrocytes, 4,870,000; leukocytes, 7,800, and hemoglobin, 83 per cent. The Wassermann reaction of the blood was negative.

A tentative clinical diagnosis of a possible congenital absence of the left kidney was made. The possibility of tuberculosis and ureteral stricture was also considered, and exploration of the left kidney was deemed advisable.

Operation.—On February 23, under general gas and ether anesthesia, the left kidney region was explored through a curved lumbar extraperitoneal incision. The left kidney was found to be a very small organ about the size of a lemon and

* Submitted for publication, July 14, 1931.

* From the Department of Pathology of the Missouri Baptist Hospital and Washington University Medical School.

slightly adherent to the surrounding fat. It was readily shelled out, causing very little trauma to the adjoining soft tissues. The renal artery was found partially occluded near the hilus of the kidney, and very little blood could be felt pulsating through it. Following the division of the ureter and ligation of the pedicle, the kidney was removed without trouble. A rubber drainage tube was inserted in the wound and the latter closed in the usual manner. There followed an uneventful convalescence, and the patient left the hospital three weeks after operation.

Pathologic Examination.—*Macroscopic Examination:* The kidney was a very small organ measuring 6 by 3.5 by 2.5 cm. The capsule was considerably thickened and strongly adherent to the cortex, rendering decapsulation practically impossible. The external surface of the kidney was mostly uniform in outline; it showed a number of punctate hemorrhages, most marked in the region of the lower pole. On hemisection of the organ, the renal parenchyma was found to be practically obliterated. The cut surface was of an opaque grayish-white luster, with a complete loss of all recognizable renal tissue. The normal configurations of the kidney could not be distinguished, and it appeared as if the entire organ was the seat of an infarct. Scattered through the parenchyma there were found occasional isolated areas that grossly appeared like carcinomatous tissue, although it was not very certain that they consisted of this type of tissue. The pelvis was moderately thickened, but otherwise was smooth and not ulcerated. No evidence of calculi or gross infection was noted in the kidney specimen.

Microscopic Examination: The greater portion of the renal parenchyma was necrotic, and no recognizable renal tissue could be made out. Amid these areas of necrosis there were found small hemorrhages which were most pronounced at the periphery immediately underneath the capsule. In other areas, there were still present occasional tubules and glomeruli of apparently normal histologic appearance, while in other portions of the kidney, there were small localized areas of cancerous growth. The latter consisted everywhere alike of typical squamous cell carcinoma, characterized by the formation of whorls of flat epithelium with pearl formation. In parts, the cancer cells were closely packed and tended to form little nests without any pearl formation. The greater part of the cancer-bearing portion of the kidney, however, was necrotic and infiltrated by a variable number of inflammatory cells. The main branch of the renal artery was invaded by cancerous tissue, the latter penetrating the entire thickness of the wall and completely occluding its lumen. The smaller ramifications of this artery were also occluded by cancerous thrombi in a manner similar to that seen in the main renal artery. The extensive necrosis of the kidney was undoubtedly the result of the thrombotic occlusion of the renal artery and its branches by cancerous growths. The pathologic changes noted in the kidney were alike in both the parenchyma and the pelvis. It was impossible to tell, therefore, even from the microscopic examination of the specimen, the exact source of origin of the tumor growth. In all probability, however, the tumor arose in the epithelium of the pelvis which had undergone squamous metaplasia. The accompanying photomicrographs (figs. 1 to 4) illustrate the histology of the neoplasm and of the diseased renal parenchyma.

Comment.—The pathologic changes noted in this kidney are of great interest. In the first place, the invasion of the renal artery by the tumor, which thus shut off the circulation to the organ, caused the destruction not only of the remaining healthy kidney tissue, but of the tumor growth itself. This resulted in a complete arrest and further spread of the tumor to local and distant organs. Clinically, there was no evidence of any metastatic growth in other organs, although metastasis might nevertheless be present in such a minute and obscure form as to escape all clinical

detection. To the date of writing this paper, however, the patient is free from any symptoms, and does not show any clinical evidence of tumor metastasis. In the second place, the absence of stones and evidence of chronic inflammation in the kidney is also worth mentioning because of their very frequent participation in the development of metaplasia and carcinoma of the kidney.

COMMENT

Squamous cell carcinoma of the urinary tract is not infrequent. This is evidenced by the evergrowing series of cases reported in the

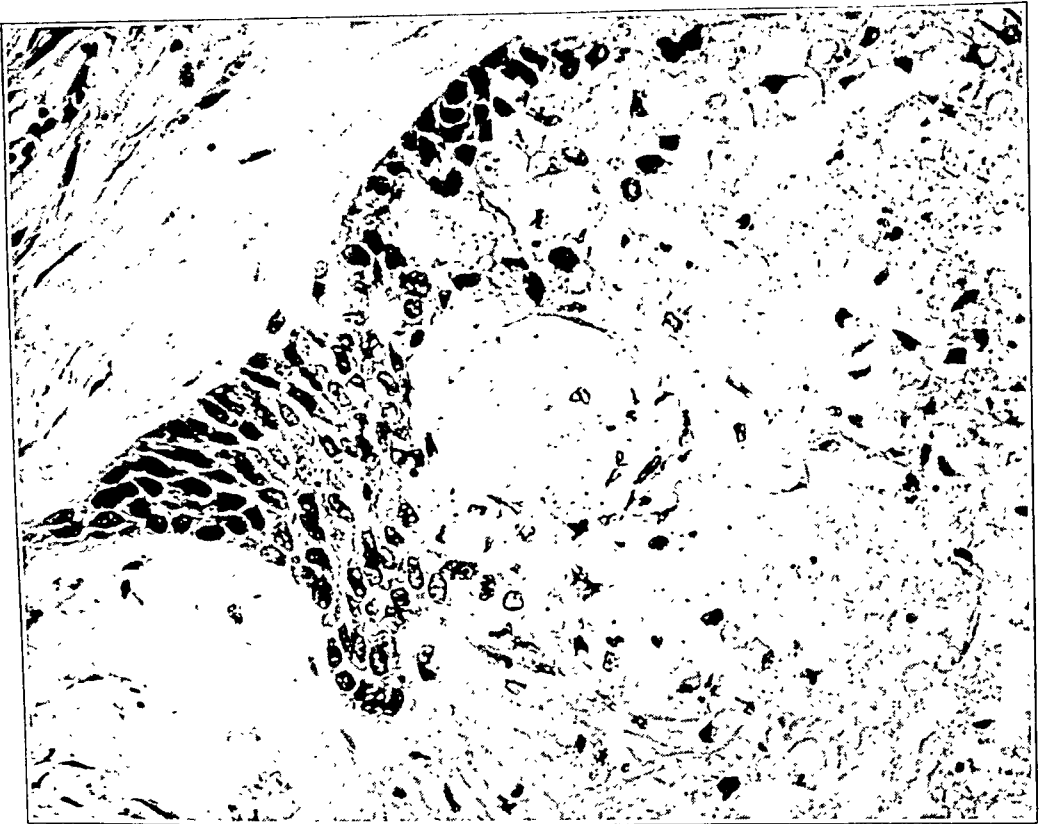


Fig. 1.—Renal tumor showing a small patch of squamous cell carcinoma. The greater portion of the renal parenchyma was necrotic and almost beyond anatomic recognition. On close examination, some of the glomerular shadows can be made out as very faint outlines.

literature. Its chief interest, however, lies not in its relative infrequency but rather in the mechanism of its formation. It has therefore stimulated considerable interest and has been the subject of a great deal of literature. Although there still exists a great deal of confusion and controversy as to the exact mechanism concerned in the development of metaplastic changes in the urinary tract, certain facts have been established that serve in many instances to explain this process. In view of all the data now available on the subject, it seems reason-

able to assume that some form of irritation, resulting from either long continued chronic inflammation or stone formation, is responsible for the metaplastic changes and the tumor growth.

Just as in cancer of the skin and certain mucous surfaces, leukoplakia is recognized as being definitely precancerous, so too in the kidney, leukoplakia, and perhaps also papilloma, constitute important predisposing factors in the development of squamous cell carcinoma.

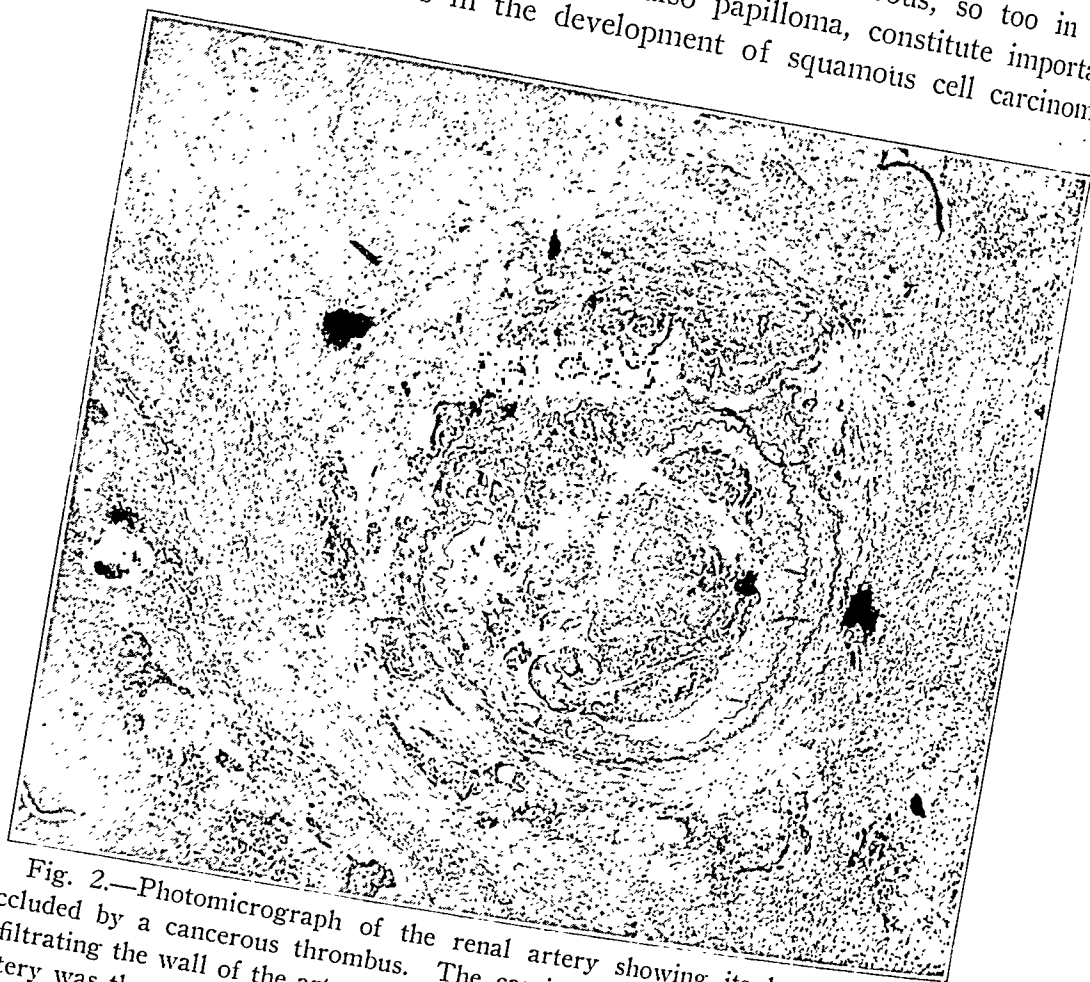


Fig. 2.—Photomicrograph of the renal artery showing its lumen completely occluded by a cancerous thrombus. The carcinomatous tissue could be seen also infiltrating the wall of the artery. The renal parenchyma surrounding the occluded artery was the seat of an extensive infarct.

Orth,¹ Beselin,² Hallé³ and Kretschmer⁴ have written convincingly on this point. These authors have found evidence of leukoplakia in kidneys that were associated with squamous cell carcinoma. Kretschmer expressed the belief that the presence of stratified squamous cell car-

1. Orth, J.: *Pathologische anatomische Diagnostik*, ed. 8, Berlin, A. Hirschwald, 1917, p. 841.
2. Beselin, O.: *Virchows Arch. f. path. Anat.* **99**:289, 1885.
3. Hallé, N.: *Ann. d. mal. d. org. génito-urin.* **14**:577, 1896.
4. Kretschmer, H. L.: *Leukoplakia of Kidney Pelvis*, *Arch. Surg.* **5**:348 (Sept.) 1922.

cinoma in the kidney and bladder can be explained on the basis of metaplasia with leukoplakia formation, and he cited two such cases to illustrate his contention. Battle,⁵ on the other hand, described epidermoid changes in small villous growths of the kidney, while Rhode,⁶ Scheel⁷ and Menetrier and Martinez⁸ described combinations of papilloma and squamous cell carcinoma. It must be remembered, however, that not all cases of squamous cell carcinoma in the urinary tract are

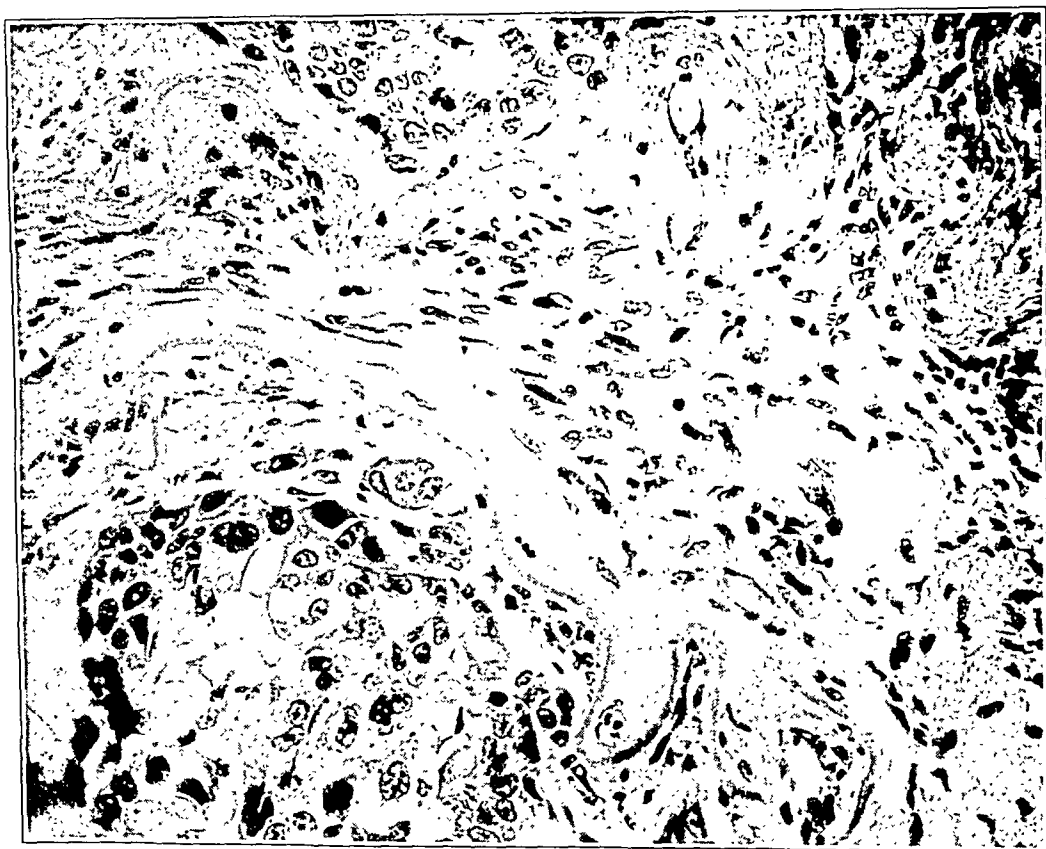


Fig. 3.—High power photomicrograph of the same artery as that in figure 2 showing the carcinomatous tissue within the wall and lumen of the artery.

preceded or accompanied by leukoplakia and papillomatous changes. In many instances such processes are entirely lacking.

Of greater interest and importance in the discussion of metaplasia is the consideration of the various etiologic factors that are believed to be responsible for the heteroplastic epithelial changes. It is almost universally acknowledged that irritation resulting from either calculi

5. Battle, W. H.: *Brit. M. J.* **1**:1206, 1895.

6. Rhode, C.: *Beitr. z. path. Anat. u. z. allg. Path.* **65**:573, 1919.

7. Scheel, P. F.: *Virchows Arch. f. path. Anat.* **201**:311, 1910.

8. Menetrier, M., and Martinez, M.: *Bull. Acad. de méd., Paris* **79**:65, 1918.

or long continued chronic inflammation may in the course of time stimulate such changes in the urinary tract. These theories are largely based on the fact that metaplastic changes and malignant transformation of the tissues are frequently associated with calculi and inflammatory lesions. This same association of metaplastic squamous cell tumors with calculi and chronic infections holds true in other organs, such as the gallbladder. Richey⁹ found that repeated trauma when continued over a long period will produce malignant alterations in the tissues involved.

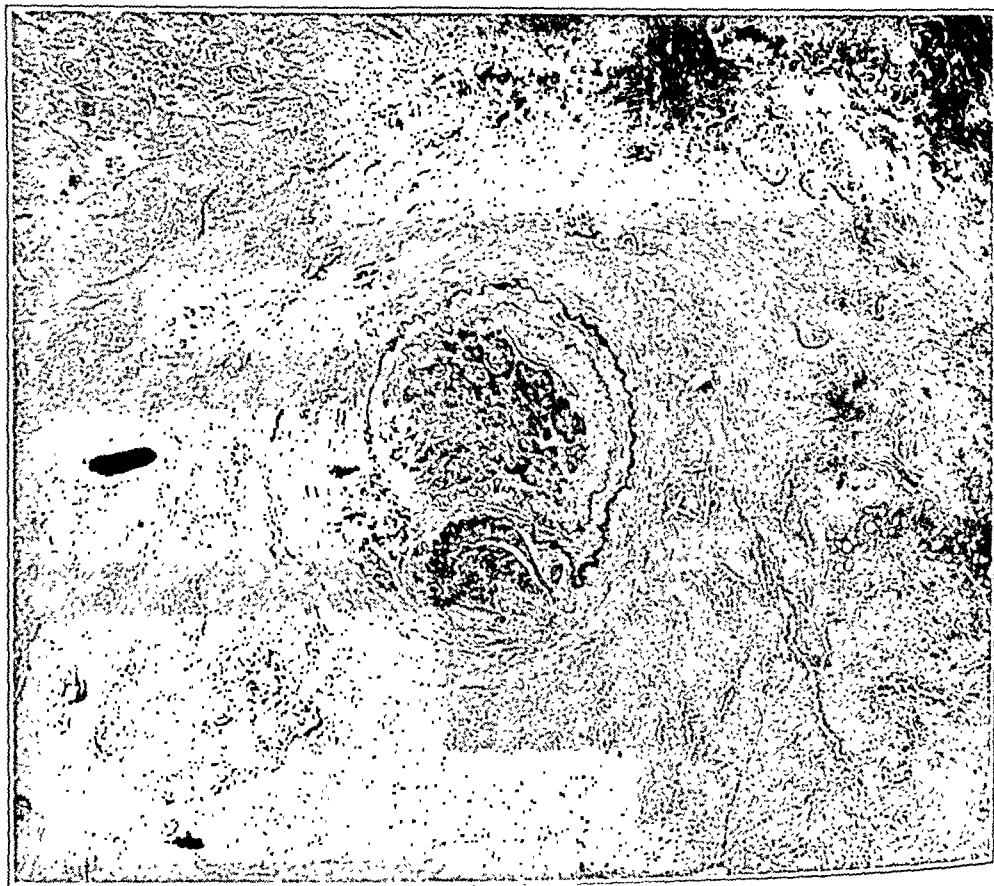


Fig. 4.—Section stained with Mallory's elastic tissue stain. It shows the tortuous elastic layer of the renal artery completely encircling the vessel and the cancerous growth within its lumen.

Scholl¹⁰ reported five cases of squamous cell carcinoma of the renal pelvis, four of which were associated with stones. The calculi in three of the kidneys were very large. Wells¹¹ reported a case of squamous cell carcinoma of the kidney that was accompanied by very large branching stones. He considered the latter as being responsible for the

9. Richey, G.: *J. Lab. & Clin. Med.* 5:635, 1920.

10. Scholl, A. J.: *Ann. Surg.* 80:594, 1924.

11. Wells, H. G.: *Carcinoma of Kidney as Sequel of Calculi*, *Arch. Surg.* 5:356 (Sept.) 1922.

pathologic process in the kidney. I¹² have found a similar instance in the gallbladder, namely, the presence of a squamous cell cancer in association with numerous stones.

While calculi and chronic infection are often found with neoplastic changes, there still remains the possibility that the latter are only secondarily superimposed on the primary malignant process. However, the long duration of symptoms of calculi and infections, which in most cases antedate those of the malignant condition, indicates that the presence of stones and inflammatory lesions precede the development of carcinoma by many years. Thus, in 108 cases of associated renal calculi and malignant conditions collected by Martin and Mertz, the symptoms of stones averaged nineteen years in duration; the symptoms suggestive of the malignant conditions averaged only five months. On the other hand, there are instances reported in the literature in which no evidence of calculi or inflammation was found in association with the neoplasm. Such are the case reported by Wendel and the one reported in this paper. There are still other investigators who believe that metaplastic changes are due to congenital anomalies caused by a disturbance in the development of the urinary tract. Lecène¹³ stated that embryologically it is an easy matter to explain heterotopia of the ectodermic cells in the vicinity of the mucosa of the upper urinary apparatus, and the fact that this may occur is sufficient to account for the lesions of leukoplakia. Leber¹⁴ reported a case of leukoplakia in the kidney of an infant 4 months old; evidence of leukoplakia was also noted in the eye of this child. The author considered this change to be a result of some congenital maldevelopment.

It is evident from the foregoing review of the literature that of the various theories that have been advanced to explain cell metaplasia and new growth, greatest emphasis has been placed on irritation resulting from either chronic inflammation or calculi as the important etiologic factor. There still remains, however, a group of cases in which no demonstrable evidence of irritation of any sort is found to account for these changes, and hence another etiologic factor must be sought to explain the pathologic process in these cases. It is quite possible that other agents besides irritants are capable of producing similar changes, although the exact nature of these is still obscure and unknown to us. It seems to me, however, that a more logical explanation for the causation of cell metaplasia and the associated new growths can be derived from the following consideration of facts.

Krompecher,¹⁵ in his extensive studies on cell metaplasia, came to the conclusion that the basal layer of cells that form the lining of certain

12. Rabinovitch, J., and Kieffer, R. S.: *Surg., Gynec. & Obst.* **52**:831, 1931.

13. Lecène, P.: *J. d'urol.* **2**:129, 1913.

14. Leber, T.: *Deutsche med. Wchnschr.* **13**:206, 1884.

15. Krompecher, E.: *Beitr. z. path. Anat. u. z. allg. Path.* **72**:163, 1924.

organs is multipotent, and, as such, is capable of developing into either cylindric or squamous epithelium. According to his view, then, the fully developed epithelial cells that line the mucosa of such organs as the uterus, stomach, intestine, etc., have their origin in a more primitive and embryonic cell layer situated deeper in the mucosa. He termed this the basal layer of cells. I feel that the term basal is a misnomer, because it carries an erroneous interpretation of the facts to many readers, although I quite agree with Krompecher that the already developed and mature epithelial cells have had their origin in a precedent embryonic type of epithelium. I also believe that this so-called primitive embryonic cell is multipotent and capable of developing into either cylindric or squamous epithelium as the case may be. If this assumption is correct, it would not be surprising to find squamous epithelium in places where cylindric epithelium is normally wont to occur. It is of particular interest to note in this connection some of the observations recorded by Wells,¹¹ which may be quoted as follows:

The formation of metaplastic squamous cell epithelium brings forward two puzzling topics, one chemical, the other embryologic. The chemical peculiarity is that squamous epithelium is characterized by the formation of keratin, which is a definite chemical compound, formed normally, as far as is known, only by the cells of ectodermal origin, including the neurokeratin of the central nervous system. When cells of endodermal origin, such as those lining the gallbladder, or those of mesenchymal origin, such as those lining the renal pelvis or the uterus, take on the function of forming this peculiar, insoluble, sulphur-rich, indigestible, protective chemical keratin, they have assumed a chemical function which seems to be far removed from their normal capacity. Hence we must conclude that metaplasia involves not only a morphologic, but a chemical transformation in the cells.

In the light of such observations, it seems that a more rational explanation for the morphologic and chemical properties of metaplastic cells can be gained, if one considers the fact that a common type of cell gives rise to both the normal and the heterologous epithelium. In other words, I believe that Krompecher's theory of cell metaplasia can also be applied in the case of the urinary tract. Just as in the case of the uterus, stomach, intestine, etc., so too in the case of the urinary apparatus there exists a primitive type of cell that is multipotent and capable of developing into either transitional or heterologous squamous epithelium. Under normal physiologic conditions only transitional epithelium is formed, but under abnormal pathologic conditions, such as may occur in the presence of inflammation and stone formation, the flat squamous epithelium may be stimulated to grow. Depending on the tempo of growth of the latter type of epithelium, there may form either a benign leukoplakia or a more malignant squamous cell carcinoma. If the primitive embryonic cells, therefore, possess the potentialities for the production of squamous epithelium as well as other varieties of epithelium, it is unnecessary to postulate cell rests of primitive tissue

at the site of the growth in order to explain these aberrant cells. The occurrence of keratin in the heterologous growth is merely the expression of the capabilities of the cells toward the formation of peculiar chemical compounds and heterologous types of epithelium when exposed to an adequate stimulus.

The circulatory disturbances that occurred in the kidney in the case reported in this paper are of particular interest and of great pathologic significance. A careful review of the literature has failed to reveal a similar instance. Taddei¹⁶ reported a case in which the vena cava was occluded by a cancerous thrombus, the tumor reaching the vena cava through the renal vein. No instances have been reported in which the nutrient vessel to the kidney has been obstructed by a malignant growth such as occurred in this case. The cancerous extension of the tumor into the artery is well illustrated in the accompanying figures (figs. 2 and 4). One can see here the tumor growth surrounding the artery and also its presence within the wall and lumen of the vessel, which latter it completely occludes. The extensive necrosis of the kidney is undoubtedly the result of the interference with the circulation to the organ produced by the cancerous thrombosis of the main arterial supply and its smaller ramifications. It is of interest to note in this connection that complete obstruction of the renal artery due to any cause is a rare condition; consequently, also complete infarction of the kidney is a rarity. There are still a number of pathologists who maintain that total infarction of the kidney hardly ever occurs. This case is therefore of unusual interest and illustrates that such a possibility may sometimes exist.

Another interesting feature of this case is the fact that the impediment to the flow of blood to the diseased kidney caused the destruction not only of the remaining healthy renal tissue, but of the tumor growth itself. The beneficial effects to the organism resulting from such tumor necrosis are quite obvious. The very extensive infarction of the kidney caused by the lack of nutrition was probably also the cause of preventing the spread of the tumor to other organs. The tumor, therefore, while infiltrating the renal artery and producing a complete infarction of the kidney, also caused its own destruction and thus saved the organism from the ravages that the malignant growth would otherwise have produced. One might say, then, that the invasion of the artery by the tumor effected a relative cure of the patient in that further spread and growth of the tumor were inhibited.

SUMMARY

A case of squamous cell carcinoma of the kidney is reported. The most interesting features of the case are the invasion of the renal

16. Taddei, D.: *Folia urolog.* 2:303, 482 and 638, 1908.

artery by the tumor and the occlusion of its lumen. This resulted in complete infarction of the kidney. Similar instances of total occlusion of the renal artery by a cancerous thrombus have not heretofore been reported in the literature. This finding renders this case, therefore, unique and of sufficient interest to make it worth reporting. The various phases of cell metaplasia are also discussed.

NOTE.—Dr. W. M. Winn gave permission for the publication of this case.

THE EFFECT OF HYPERTONIC SOLUTIONS ON CEREBROSPINAL FLUID PRESSURE

WITH SPECIAL REFERENCE TO SECONDARY RISE AND TOXICITY *

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AND

PAUL HURWITZ, B.S.

CHICAGO

This investigation has been undertaken in an endeavor to study the course of the spinal fluid pressure following the intravenous injection of hypertonic solutions.

Of special interest was the recurrence of pressure symptoms and occasional death after apparent clinical improvement in cases of increased intracranial pressure in which treatment with intravenous hypertonic solutions was used, as pointed out by Browder¹ and Foley.²

One man and a series of dogs were studied with regard to the effect of hypertonic solutions on the spinal fluid pressure.

In 1901, Cannon³ formulated the theory of the mechanism of cerebral edema, essentially as follows:

1. Edema causes pressure on the vessels, which is transmitted to the arteries and veins, causing an increased blood pressure, with increased transudation and further increase in blood pressure, resulting in a vicious circle leading ultimately to anemia of the brain from vascular compression.

2. At the moment of injury intracranial pressure rises to a height sufficient to check blood flow to the brain.

This is substantiated by recent investigations demonstrating that fluid exuded from injured cerebral tissue has an increased osmotic pressure.

Cannon concluded that secondary increase of spinal pressure is due to three factors: (1) deprivation of normal nutrition to the injured parts; (2) passage of fluid with the subsequent swelling of these parts, and (3) rigid enclosure of the brain, which causes the swelling of one region to affect markedly the rest of the brain.

* Submitted for publication, June 5, 1931.

* From the Department of Pathology, University of Illinois.

1. Browder, Jefferson: Dangers in the Use of Hypertonic Salt Solutions in the Treatment of Brain Injuries, *Am. J. Surg.* 8:1213, 1930.

2. Foley, F. E. B.: Clinical Uses of Salt Solutions in Conditions with Increased Intracranial Tension, *Surg., Gynec. & Obst.* 33:126, 1921.

3. Cannon, W. B.: Cerebral Pressure Following Trauma, *Am. J. Physiol.* 6:91, 1901.

Early investigators felt that the brain was incompressible, and when later Weed and McKibben⁴ found that brain fluid volume and cerebrospinal fluid volume around the brain could be reduced by the intravenous injection of hypertonic solutions of sodium chloride, Ringer's solution, sodium bicarbonate, sodium sulphate and dextrose, it was thought that a great advance was made in the alleviation of pressure symptoms.

Following this, Cushing and Foley⁵ and Foley and Putman⁶ demonstrated the effective reduction in spinal fluid pressure by oral ingestion and rectal and intra-intestinal administrations of hypertonic sodium chloride and dextrose.

Relief from pressure symptoms was obtained clinically in some instances by Foley, and Sachs and Malone.⁷

Falkenheim and Naunyn⁸ stated that spinal fluid pressure varies with arterial pressure; Becht⁹ showed that it varies with venous pressure; Foley and Putman⁶ demonstrated a rise in blood pressure with a fall in spinal pressure, and efforts were made to reduce spinal fluid pressure by varying these influencing factors.

However, results obtained experimentally were not substantiated clinically, and Fay¹⁰ investigated the relative value of repeated doses of magnesium sulphate, which, however, has the disadvantage of its purging effect.

Esbaugh and Stevenson¹¹ demonstrated the transient effect of salt solution in decreasing spinal pressure. They also showed a secondary increase in spinal pressure, which is attributed to the diffusion of salt into the cerebral tissues. They further concluded that intravenous injections of dextrose are more effective, because of the longer diffusion time.

4. Weed, L. H., and McKibben, P. S.: Pressure Changes in Cerebrospinal Fluid Pressure After Intravenous Injections of Solutions of Various Concentrations, *Am. J. Physiol.* **48**:512, 1919; Experimental Changes in Brain Bulk, *ibid.* **48**:531, 1919.

5. Cushing, H., and Foley, F. E. B.: Alterations of Intracranial Tension by Salt Solutions in the Alimentary Canal, *Proc. Soc. Exper. Biol. & Med.* **17**:217, 1920.

6. Foley, F. E. B., and Putman, T. J.: The Effect of Salt Ingestion on Cerebrospinal Fluid Pressure and Brain Volume, *Am. J. Physiol.* **53**:464, 1920.

7. Sachs, E., and Malone, J. Y.: The Use of Hypertonic Salt in Experimental Increased Intracranial Pressure, *Am. J. Physiol.* **55**:277, 1921.

8. Falkenheim, H., and Naunyn, B.: Ueber Hirndruck, *Arch. f. Path. u. Pharmacol.* **22**:261, 1887.

9. Becht, F. C.: Studies on Cerebrospinal Fluid, *Am. J. Physiol.* **51**:1, 1920.

10. Fay, T.: Comparative Values of Magnesium Sulphate and Sodium Chloride, *J. A. M. A.* **82**:766 (March 8) 1924.

11. Esbaugh, F. G., and Stevenson, G. S.: The Measurements of Intracranial Pressure Changes in an Epileptic and Its Experimental Variations, *Bull. Johns Hopkins Hosp.* **31**:440, 1920.

In an attempt to eliminate the factors of dialysis, Hughes and Laplace¹² used a nondiffusible substance of high osmotic pressure (sodium arabinatate) to some advantage.

The possible toxicity and even death due to the intravenous hypertonic sodium chloride therapy have been pointed out by Browder.¹

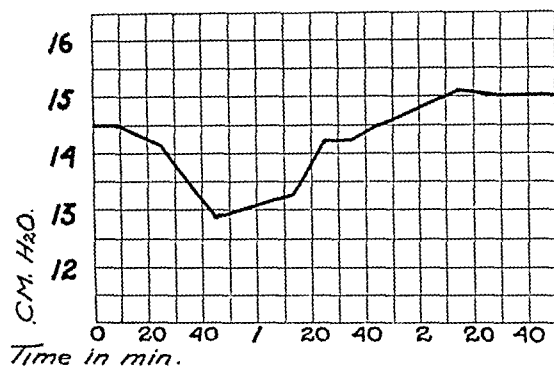


Chart 1.—Normal spinal fluid pressure of a dog in a constant prone position for three hours.

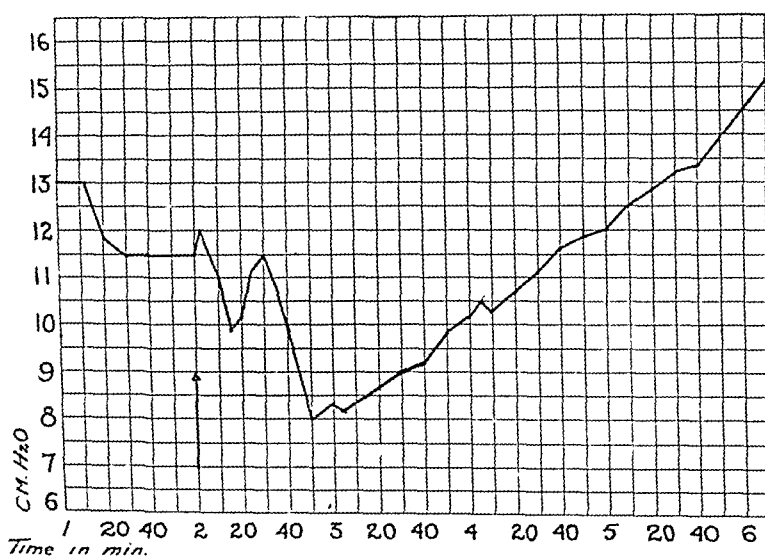


Chart 2.—The effect of 100 cc. of 50 per cent dextrose on the spinal fluid pressure.

Finally, cases of recurring stupor, coma and death in from three to four hours following the intravenous therapy have repeatedly crept into the literature.

12. Hughes, J., and Laplace, L.: Effect of Hypertonic Solutions of Sodium Arabinatate on Cerebrospinal Fluid Pressure, *J. Pharmacol. & Exper. Therap.* **38**: 363, 1930.

Because of this last fact, attention was directed to the course of spinal fluid pressure over periods of from five to eight hours continuously, in contrast to most of the investigators whose results were obtained from observations that extended from sixty to eighty minutes.

APPARATUS

The apparatus used is of special importance in that there was no loss of spinal fluid as had occurred with Weed and McKibben and others.

A fine bore U tube graduated glass manometer was attached to a short length of rubber pressure tubing. The system was then filled with physiologic solution of sodium chloride. This was connected to a spinal puncture needle in the cisterna magna, without the loss of fluid. Spinal pressure readings were made directly from the graduated manometer and also recorded on the kymograph.

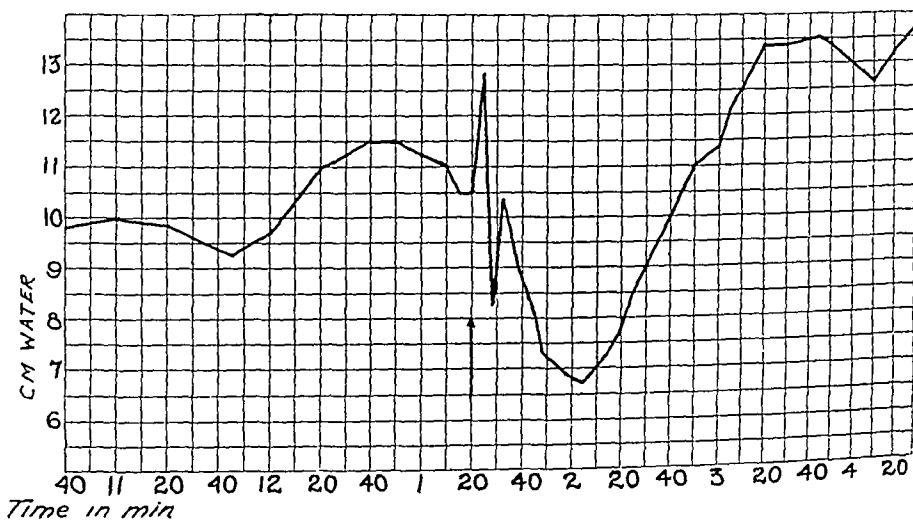


Chart 3.—The effect of 75 cc. of 50 per cent dextrose on the spinal fluid pressure.

Variations in blood pressure were graphed in the usual manner, the femoral vessel being used.

The anesthetic used, sodium ethyl barbiturate, allowed a uniform condition of anesthesia for long periods of time and thus had no influence on the spinal fluid pressure, as was demonstrated by repeated controls.

EXPERIMENTAL RESULTS

The following data and associated charts illustrate the typical reaction of the spinal fluid pressure to the various concentrations of salt and dextrose administered intravenously.

Chart 1 indicates the normal spinal fluid pressure of a dog in a constant prone position for a period of three hours. The variation is comparatively slight, showing a change of 20 mm. Other observations over varying periods of time show even lesser variation in pressure, as is indicated in charts 2, 5 and 6.

Variations, however, may occur and are indirectly influenced by changes in position, respiration and arterial and venous pressures.

The animals were watched for variable lengths of time until a constant level was established. Then the intravenous injections of hyper-tonic solutions were made by the gravity method.

Chart 2 illustrates the effect of 100 cc. of 50 per cent dextrose. This caused a slight rise in pressure of 5 mm., which was immediately fol-

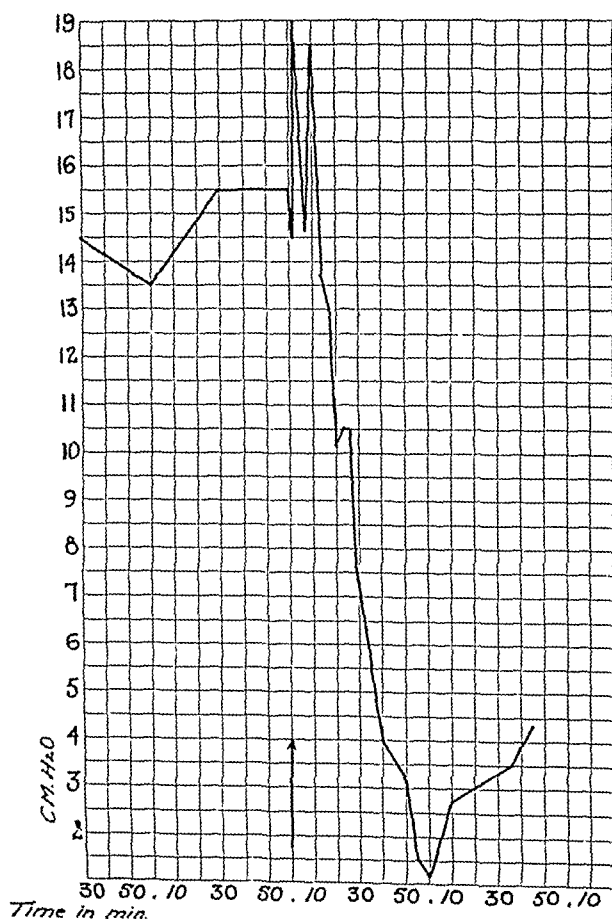


Chart 4.—The effect of 75 cc. of 30 per cent sodium chloride on the spinal fluid pressure.

lowed by a slowly decreasing pressure of 35 mm. in fifty minutes. Then followed a secondary rise with a gradual return to the normal level in two hours, showing an effective change in the course of two hours and fifty minutes—and effective therapy for almost three hours. However, the pressure continued to rise to a point 30 mm. above the original level within one hour or slightly longer.

Chart 3 shows the reaction following the use of 75 cc. of 50 per cent dextrose. The reaction was similar to the preceding one, except

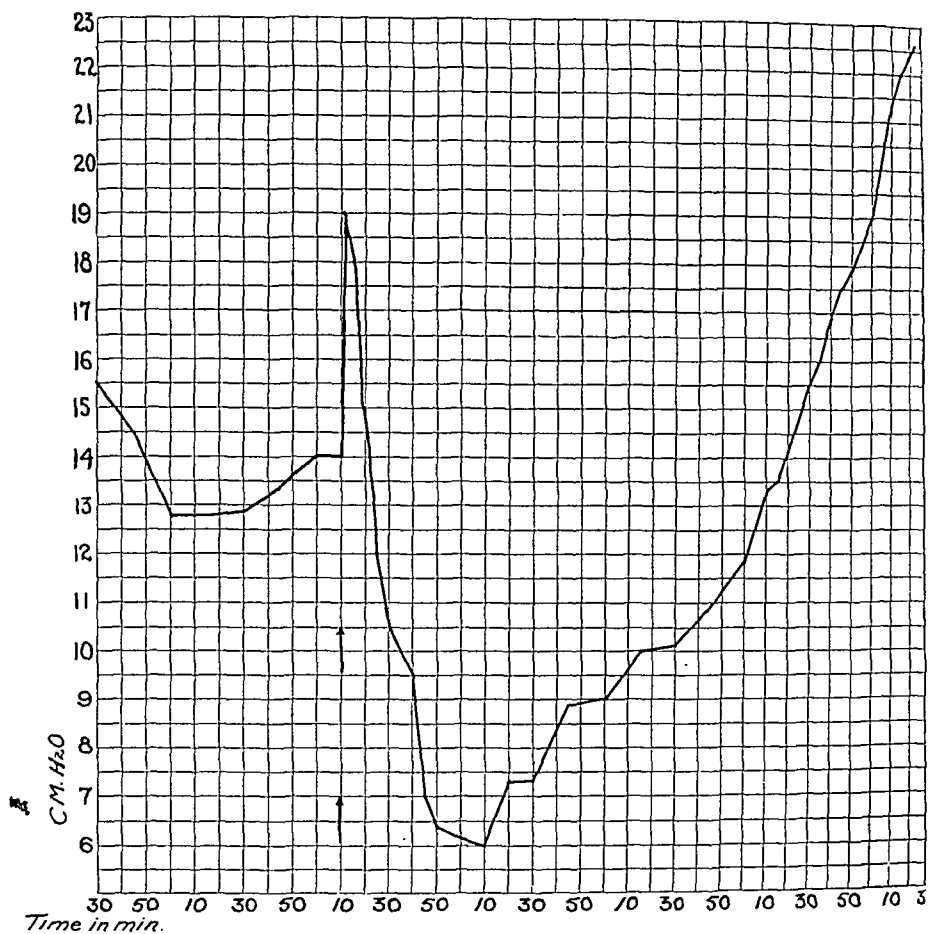
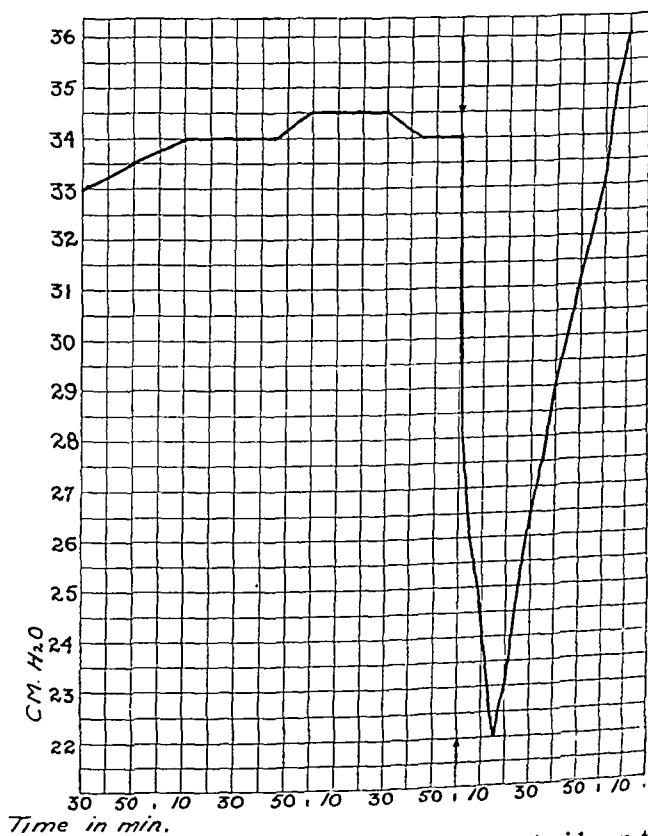


Chart 5.—The effect of 100 cc. of 15 per cent sodium chloride on the spinal fluid pressure.



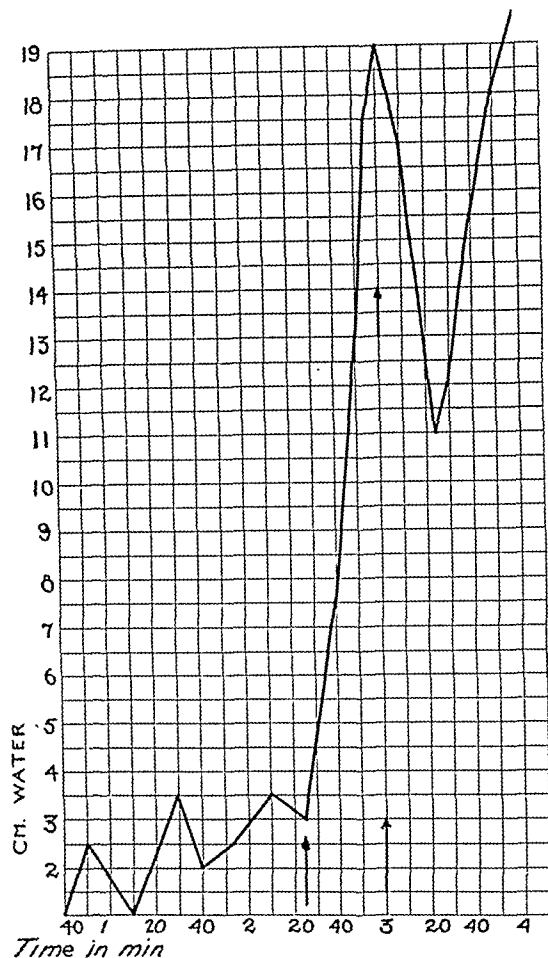


Chart 7.—The effect of an induced increase in spinal fluid pressure on a dog. Fifty cubic centimeters of 10 per cent sodium chloride was injected at the height of the curve.

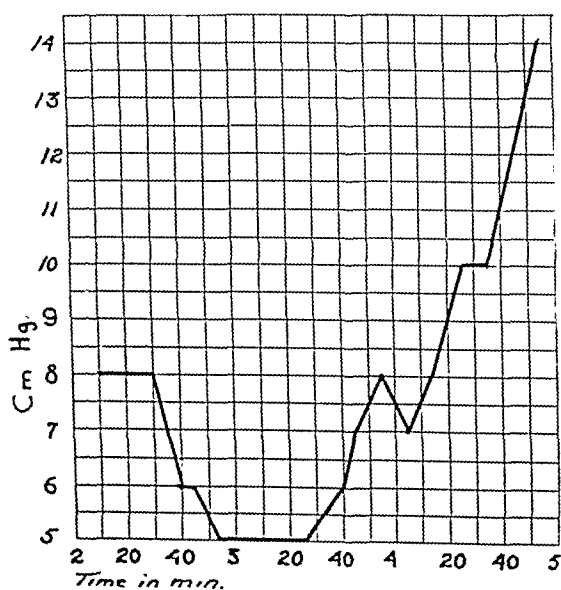


Chart 8.—The effect of 200 cc. of 50 per cent dextrose on a man, aged 57 years, with a clinical diagnosis of tabes.

that the maintenance of a lowered pressure was sustained for a shorter length of time. The drop in pressure was 37 mm., with the return to normal consuming only forty-five minutes, after the pressure had reached its lowest point. The reaction phase showed a rise of 30 mm. above normal in one hour.

Chart 4 shows the reaction following the use of 75 cc. of 30 per cent sodium chloride. There was a slight drop followed by a rise of 50 mm. of water. This was followed by a rapid fall of 160 mm. in one hour. The upward curve shows the tendency to return. At this point, however, the animal died. Although the marked toxicity of hypertonic saline solution has been demonstrated before, further emphasis of this toxicity is brought by this and subsequent experiments with the same

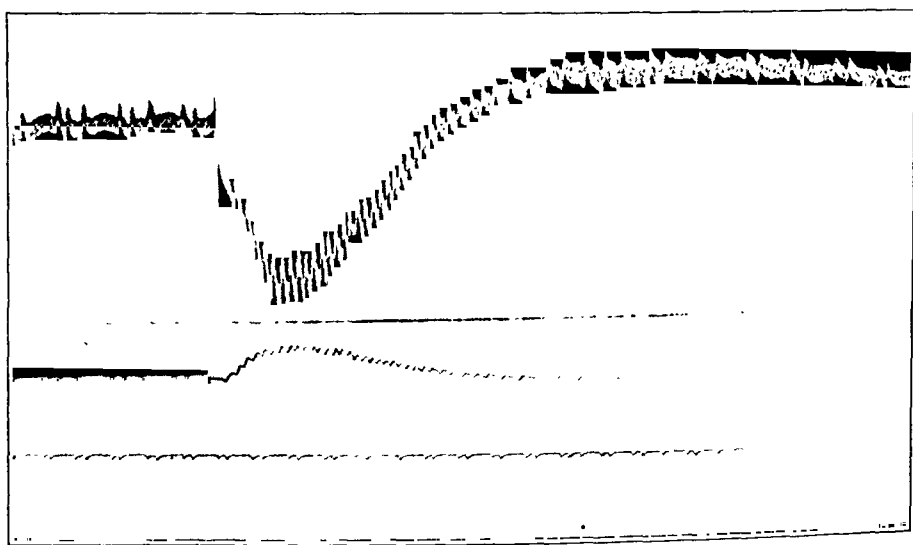


Chart 9.—Kymographic record showing the effect of an initial injection of 30 per cent sodium chloride. Note the rise in spinal fluid pressure with the simultaneous drop in arterial pressure.

concentration of salt solution which always resulted in the death of the animal.

Chart 5 shows the reaction of spinal fluid pressure to 100 cc. of 15 per cent sodium chloride. The immediate rise of 50 mm. was followed by a sudden drop of 80 mm. in one hour, after which the return to normal was concluded in two hours. In the following hour, the pressure rose 85 mm. above normal.

The effective decrease in pressure here when contrasted to that of the preceding experiment is one-half for the same length of time. This demonstrates the effect of the molar concentration of the solution.

Thus far, the results obtained present a rather striking uniformity. the drop in pressure taking place in one hour, with the rise in pressure. or secondary return to normal, consuming two hours, and the whole period of effectiveness being almost three hours. Following this is the

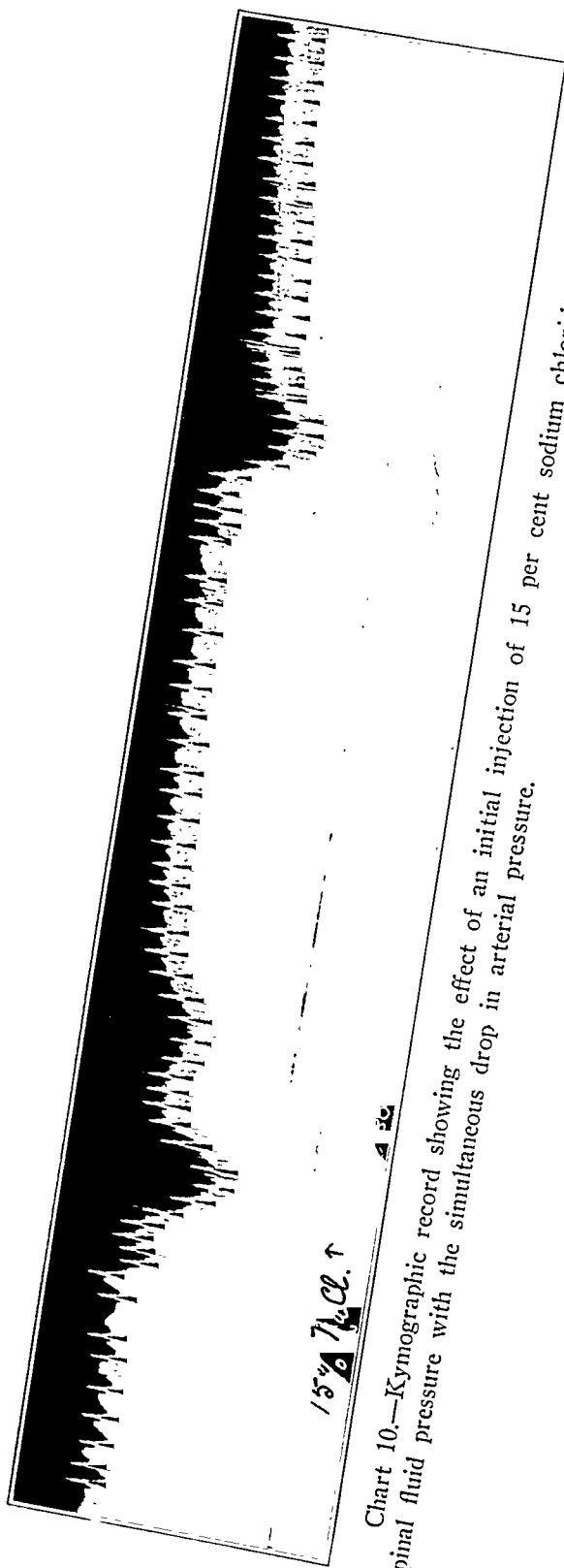


Chart 10.—Kymographic record showing the effect of an initial injection of 15 per cent sodium chloride. Note the rise in spinal fluid pressure with the simultaneous drop in arterial pressure.

period in which the spinal fluid pressure rises much above normal, the sodium chloride showing a greater action in reduction of pressure and greater reaction in the associated secondary rise.

The following experiments show the results obtained with solutions of lesser concentration.

Chart 6 shows the reaction following the use of 50 cc. of 10 per cent sodium chloride. The rather sudden drop in pressure of 120 mm. in fifteen minutes, the secondary rise to normal in fifty minutes and the secondary reaction with the rise of 20 mm. above normal in eight minutes are shown. This illustrates an effective therapy of only sixty-five minutes.

Concentrations of 25 per cent dextrose showed a similar effect but with a more shallow curve.

Chart 7 shows the results obtained on a dog with an induced increase in spinal fluid pressure. The injection of 50 cc. of 10 per cent sodium chloride at the height of the curve shows the transient effect of the solution. The return to the original height was accomplished in fifty-five minutes. Evidence of pressure symptoms becomes apparent, with a resultant relaxation of the sphincter ani.

Small concentrations of dextrose show but negligible variations.

Chart 8 represents the results of the observations in the case of a man 57 years of age with a clinical diagnosis of tabes. The decrease in pressure indicates the action of 200 cc. of 50 per cent dextrose. A drop of 3 mm. of mercury is seen, which was sustained for one hour. Following this was the typical secondary rise, which in one and a quarter hours was 6 mm. of mercury above the original level of 8 mm. of mercury.

An incidental finding is the relation of the initial rise in spinal fluid pressure to the arterial pressure. With the increase in spinal pressure is seen a simultaneous drop in the arterial pressure, as is shown in the kymograph record (charts 9 and 10).

COMMENT

The occasional primary rise in spinal fluid pressure immediately after the injection of hypertonic salt solution is associated with a drop in blood pressure due to the toxic effect of high concentrations of saline. The subsequent fall is the result of the increased osmotic pressure of the blood. Were we dealing with a closed septum, an equilibrium would be reached. However, the excess of injected salt or dextrose is lost from the blood by excretion through the kidneys and removal into the tissues as well as passage into the spinal fluid. This results in a reversal of the original situation, giving the spinal fluid a higher osmotic pressure than the blood and resulting in the secondary rise seen uniformly in our experiments. When used in the presence of an already raised intracranial pressure, this therapy carries an obvious danger.

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SUMMARY

1. The reduction of cerebrospinal fluid pressure with single doses of hypertonic salt and dextrose is transient.
2. A secondary rise occurs which reaches a point much higher than the original level.
3. High concentrations of sodium chloride are definitely toxic.
4. In view of these facts, it is probable that recurrent pressure symptoms and the occasional deaths reported are due to the secondary rise in spinal fluid pressure.

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OSTEOGENIC SARCOMA *

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INTRODUCTION

Emphasis is repeatedly placed on the lawlessness of cancer and its defiance of growth restraint. However, the diagnostic features of the disease, the establishment of well defined clinical entities under this category, as well as the uniform gravity of the prognosis, all point to the reverse of this statement, indicating that the biology of malignancy conforms to definite and rigorous laws. The repetition to a fair degree of the design and physiology of the parent tissue by the neoplastic growth suggests that the tumor in its development repeats the normal histogenesis of the part affected. An analysis of these normal histogenetic processes, usually neglected in pathology, should therefore prove most significant in a study of the origin of various forms of tumors.

In a study of osteogenic sarcoma, which is one of the more variable tumors in which chaotic distortion of normal development has been much stressed (Putti ¹), an analysis of the underlying tumor processes in relation to the embryology of bone reveals that the normal order of osteogenesis is essentially adhered to, and that the malignant change is more of degree than of kind. When the histogenetic processes exhibited by these tumors are focused on, instead of their mere histologic appearances, the problem of analysis is greatly simplified. On such a basis it is possible to divide the malignant bone-forming sarcomas into a cartilaginous and fibro-osseous series. These two major divisions of osteogenic sarcoma correspond in a general way to the two fundamental types of osteogenesis observed in the human embryo, the intra-cartilaginous and the membranous.

In the present study, each of these two major groups of osteogenic lesions have been subdivided into early and late forms. The earlier form of cartilaginous tumor arises from precartilaginous connective tissue resembling in its behavior the blastema ² from which the cartilage of the future skeleton is derived in the human embryo. This tissue has the power of forming both cartilage and bone, and pathologically this

* Submitted for publication, May 5, 1931.

² From the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University.

1. Putti, Vittorio: Malignant Bone Tumors, Surg., Gynec. & Obst. 48:324, 1929.

2. The term blastema is used to refer to a condensation of primitive connective tissue at the site of the future skeleton immediately preceding cartilage formation in the embryo. (See fig. 6.)

loose collection of embryonic fibroblasts passing from a syncytial state into cartilage has been referred to for many years under the misnomer "chondromyxosarcoma" (fig. 1).

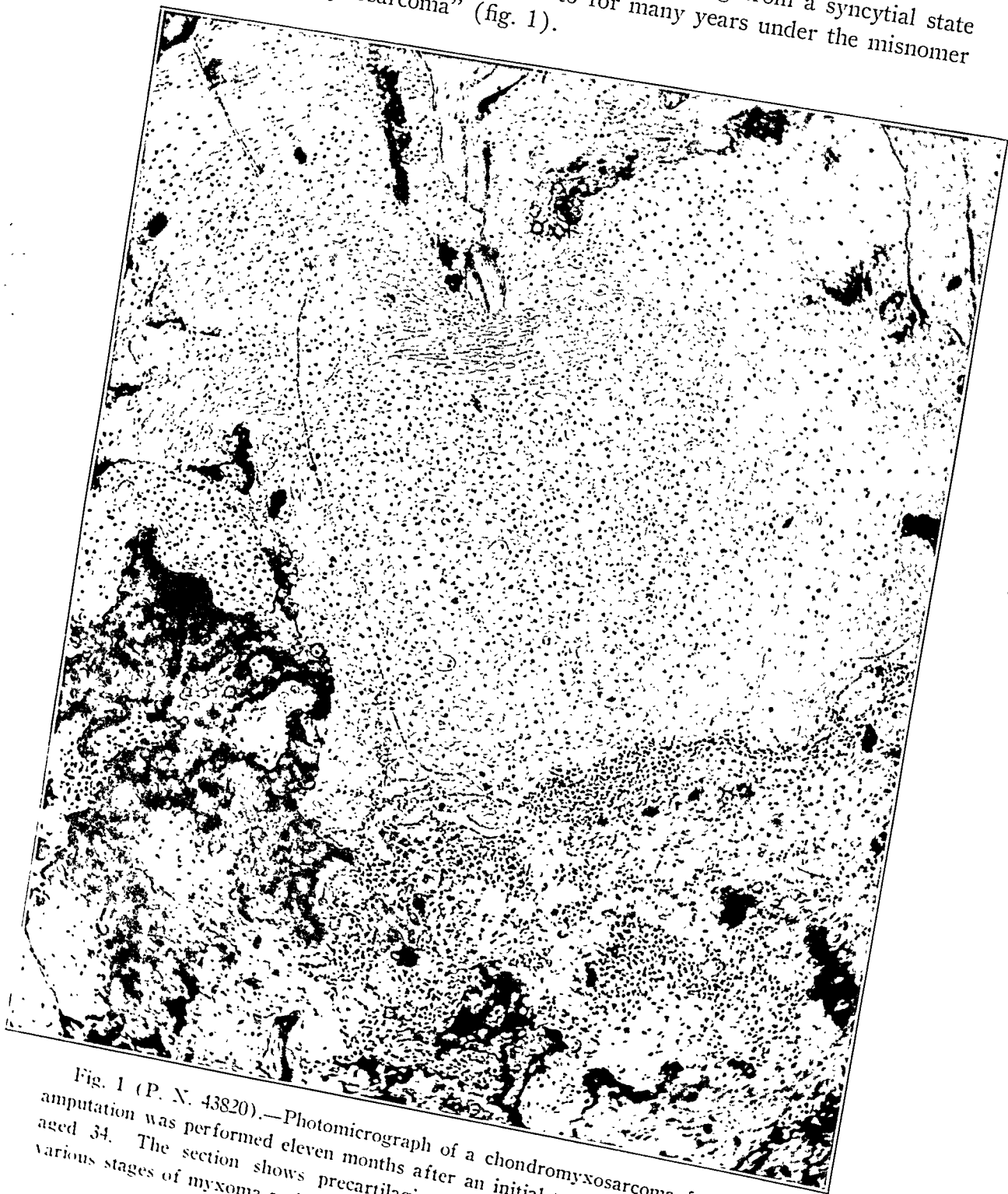


Fig. 1 (P. N. 43820).—Photomicrograph of a chondromyxosarcoma for which amputation was performed eleven months after an initial trauma, in a white man, aged 34. The section shows precartilaginous connective tissue giving rise to various stages of myxoma and cartilage. A slight amount of new bone is present.

The later form of chondral sarcoma arises from tissue that has already differentiated into cartilage and takes its source in the proliferation of chondroblasts which at puberty occurs at an unossified epiphyseal

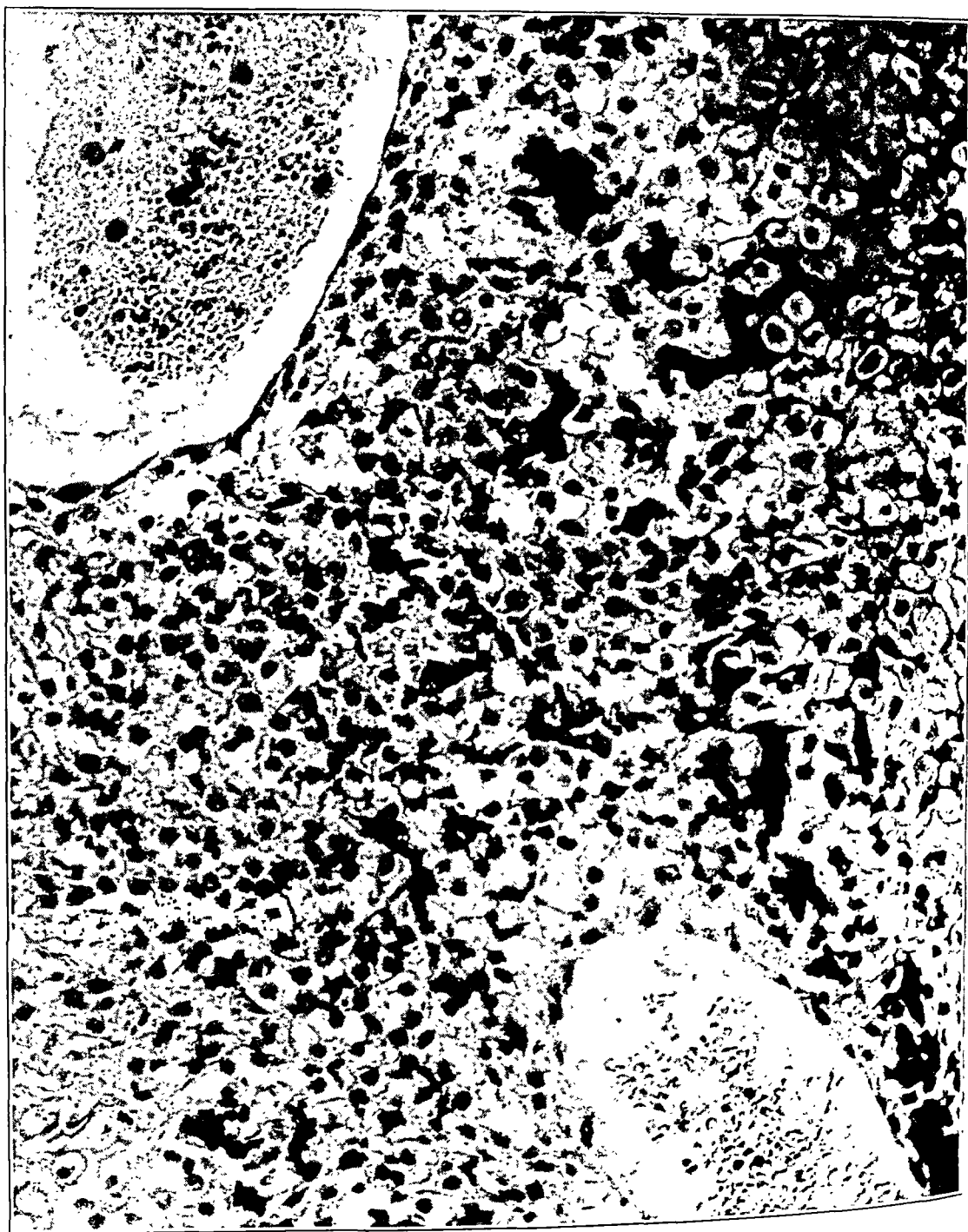


Fig. 2 (P. N. 41819).—Photomicrograph of chondroblastic sarcoma. The section shows proliferating chondroblasts giving rise to areas of cartilage undergoing calcification. The picture indicates the vascularity of this calcifying form of chondral sarcoma.

line. Histologically, the tissue transforms rapidly from a chondroblastic stage into an end-product of calcified cartilage without achieving the state of even osteoid tissue (fig. 2). A perusal of the literature shows that this form of tumor has not been widely recognized as an

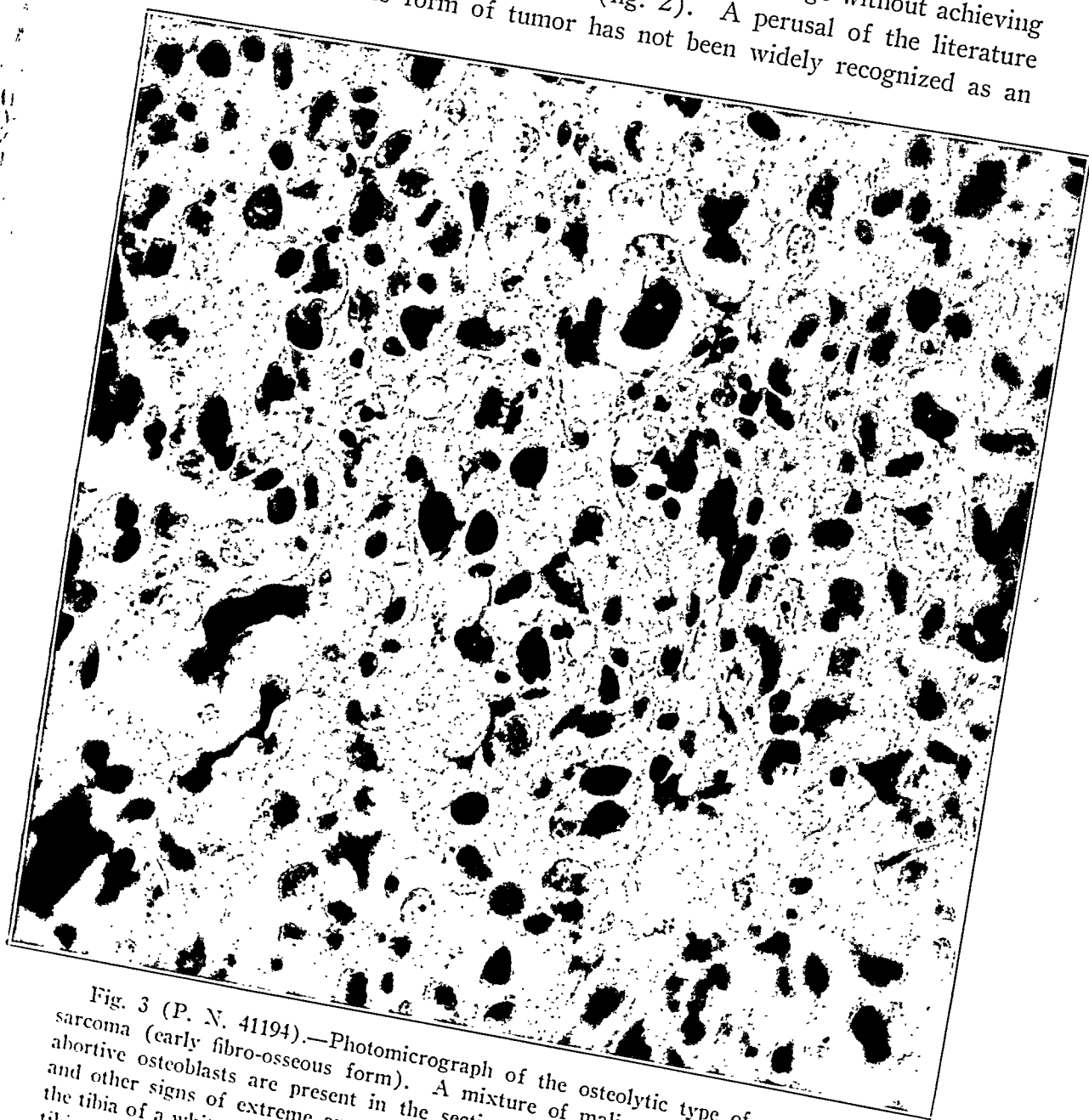


Fig. 3 (P. N. 41194).—Photomicrograph of the osteolytic type of osteogenic sarcoma (early fibro-osseous form). A mixture of malignant spindle cells and abortive osteoblasts are present in the section. There are many mitotic figures and other signs of extreme anaplasia. The tumor occurred in the upper end of the tibia of a white boy, aged 13, who had suffered a trauma in the upper end of the tibia three weeks previously.

entity heretofore and is most often confused with other tumors such as angiosarcoma and the so-called metastatic giant cell tumor of the

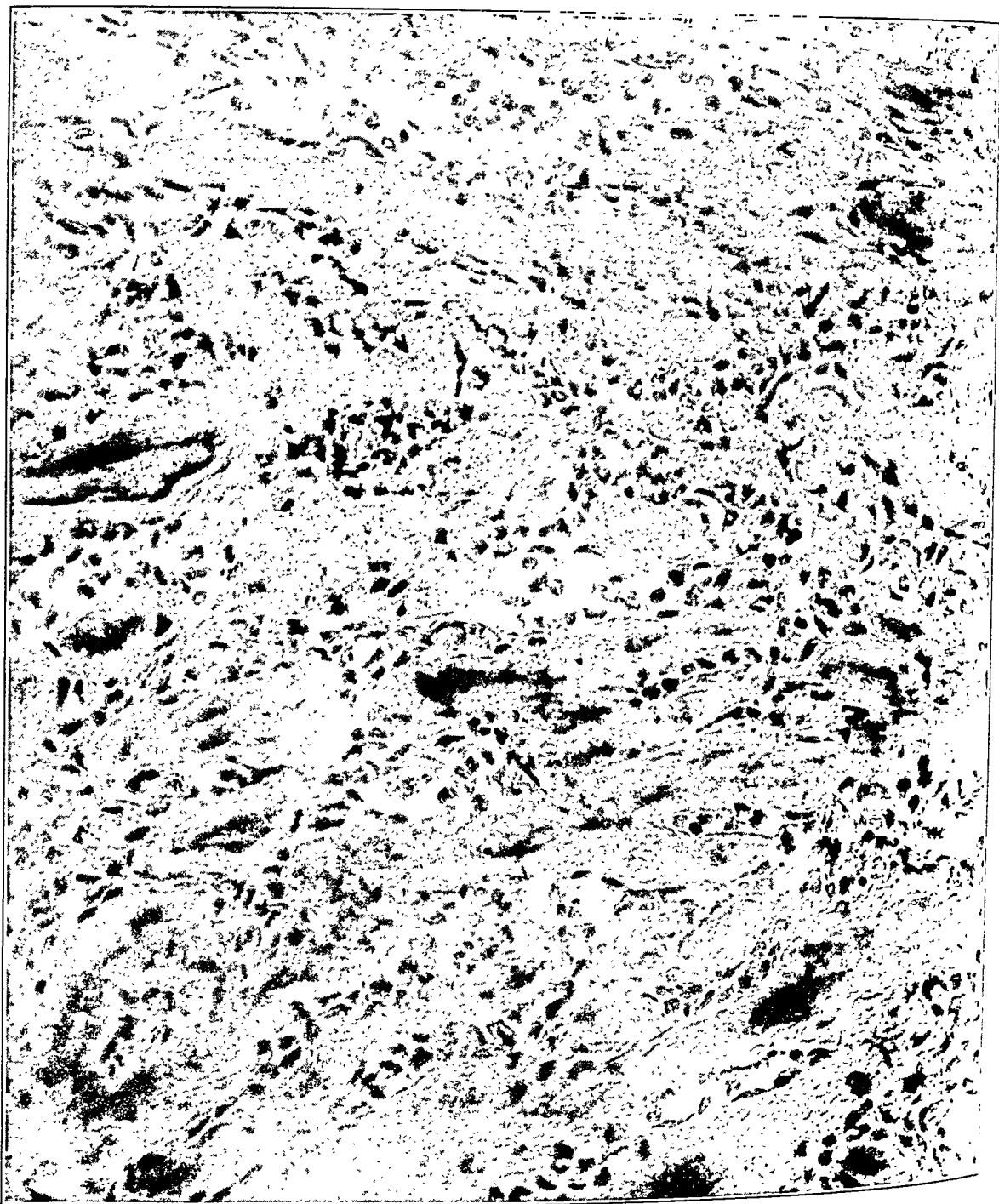


Fig. 4 (P. N. 30616).—Photomicrograph of sclerosing osteogenic sarcoma (late fibro-osseous form). Note the irregular trabeculae of new bone and osteoid material surrounded by profuse numbers of osteoblasts and spindle cells. The lesion occurred in the upper end of the femur of a white youth, aged 20, who died eighteen months after disarticulation at the hip joint.

bone (Geschickter and Copeland³), although Ziegler⁴ referred to such a case under the term "petrifying sarcoma."

The fibro-osseous series of malignant tumors, which, as a rule, do not form cartilage, may be similarly divided into an earlier and a later form. The earlier type in this group, which is related to the formation of cancellous bone, is only potentially bone-forming and is histologically composed of a mixture of large malignant spindle cells and abortive osteoblasts (fig. 3). Osseous formation is restricted in this tumor because ossification in the fibrous tissue, from which the growth takes origin, is dependent on a previous storage of calcium by cartilage, and such a storage is not available at the site and time of the malignant change. In the early literature this tumor appears under the caption of "malignant bone aneurysm" (Paget⁵).

The other form of fibro-osseous sarcoma, which is related to the formation of cortical bone, arises from fibrous tissue capable of direct osseous formation. It is characterized histologically by a rapid proliferation of osteoblasts with the laying down of much osteoid and osseous intercellular material and the formation of numerous irregular bony trabeculae (fig. 4). Since the time of Virchow⁶ pathologists have referred to it as "sclerosing" sarcoma of the bone.

This division of the malignant bone-forming tumors into a cartilaginous and fibro-osseous series, each with an early and late form, is based on an analysis of over 350 cases in the group of osteogenic sarcomas. The clinical and pathologic entities thus delineated are more uniform than the conglomerate class of tumors now referred to as osteogenic sarcoma and permit greater accuracy in the diagnosis, prognosis and methods of treatment of these lesions. While retaining the term osteogenic to refer to these sarcomas as a group, the present study endeavors to show that this factoring of malignant bone-forming tumors into four separate types rests on a sound histogenetic basis and aids materially in the comprehension of the nature of the malignant process as it appears in bone.

PART I: THE CHONDRAL FORMS OF OSTEOGENIC SARCOMA

Malignant tumors of the skeleton giving rise to cartilage have their source in more primitive structures, and have entirely different growth

3. Geschickter, C. F., and Copeland, M. M.: Recurrent and So-Called Metastatic Giant Cell Tumor, *Arch. Surg.* **20**:713 (May) 1930.

4. Ziegler, Ernst: *General Pathology*, New York, William Wood & Company, 1899, chapt. VII, p. 350, fig. 282.

5. Paget, James: *Lectures on Surgical Pathology*, London, Longmans, Green & Company, 1876, Lecture 27, p. 583, footnote 7.

6. Virchow, Rudolf: *Die krankhaften Geschwülste*, Berlin, August Hirschwald, 1864, vol. 2, chapt. 19, p. 296, fig. 154.

properties from those neoplasms arising in bone of fibro-osseous origin. These more primitive chondral growths, while having in common the power to produce cartilage vary in the modes of their origin, the type of osseous bone involvement produced and in their clinical aspects.

The earliest type of the chondral forms of osteogenic sarcoma, best known in the older literature as chondromyxosarcoma, has recently been singled out by Phemister⁷ to be dignified as a separate entity under the term chondrosarcoma in opposition to the more generalized classification of these tumors by the Bone Sarcoma Registry. A histogenetic analysis of this group of tumors is necessary if present day knowledge is to be advanced beyond the concepts of Virchow⁸ and Paget,⁹ both of whom described these very malignant tumors in some detail, but drew no sharp line of differentiation between them and the frankly benign cartilaginous neoplasms and those so-called benign chondromas with extensive growth which ultimately may prove fatal by metastases. The importance of making such a distinction necessitates a subdivision of chondromyxosarcoma into primary and secondary types. This separation into primary and secondary forms rests on the fact that while a group of very malignant chondromyxosarcomas of the periosteal type (fig. 5) arise *de novo* in young patients between the ages of 14 and 25 years, with a brief duration of symptoms, averaging less than six months, a secondary form, which generally invades the medullary cavity and which is nearly identical in histology with the first, is encountered in patients usually beyond the age of 30 years, who give a protracted history of some previous benign lesion, such as single or multiple exostoses or a central chondroma.

In arriving at these subdivisions of chondrosarcoma, a study was made of over 300 cases in the group of benign fibrocartilaginous tumors (Geschickter¹⁰), in addition to the analysis of 180 cases in the group of chondrosarcomas resummarized here. For a detailed tabulation of these cases, the reader is referred to this previous paper.

PRIMARY CHONDROSARCOMA

The primary form of chondrosarcoma is a very malignant tumor arising periosteally, which does not primarily involve either the cortex or the medullary cavity of the bone (fig. 5), and which is characterized

7. Phemister, D. B.: *Surg., Gynec. & Obst.* **50**:216, 1930.

8. Virchow, Rudolf: *Die krankhaften Geschwülste*, Berlin, August Hirschwald, 1863, vol. 1, p. 534.

9. Paget, James: *Lectures on Surgical Pathology*, 1876, Lecture 26, p. 495.

10. Geschickter, C. F.: *Fibrocartilaginous Tumors of the Bone*, *Arch. Surg.* **23**:215 (Aug.) 1931.

in the roentgenogram by its translucent and nearly invisible periosteal shadow. The distinguishing microscopic composition of loose connective tissue merging into zones of cartilage with an abundant hyaline matrix, which may be fringed by osseous tissue, signifies a special mode of origin for this tumor (fig. 1).

Contrary to Sternberg,¹¹ Kolodny,¹² Ewing¹³ and others, recent studies showed that this loose myxomatous material is not a degenera-

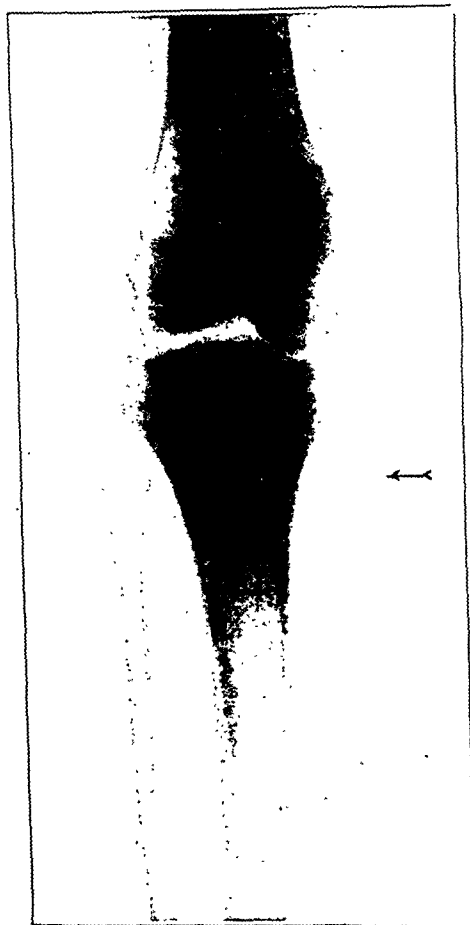


Fig. 5 (P. N. 38620).—Roentgenogram of a typical primary chondrosarcoma arising at the insertion of the quadriceps tendon in a white girl, aged 14. The picture shows a typical translucent periosteal shadow and the absence of marked medullary or cortical involvement.

tive product of these growths, but contains the mother cells of the neoplasm in the form of a primitive precartilaginous tissue from which

11. Sternberg, K.: Personal interview with the author, July, 1929.

12. Kolodny, A.: Bone Sarcoma: the Primary Malignant Tumors of Bone and the Giant Cell Tumor, Chicago, Surgical Publishing Company, 1927.

13. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

the chondral and osseous portions of the tumor are developed. This precartilaginous tissue is not far removed from the mesenchymal state in the embryo which precedes the development of the skeleton. It is, however, a normal structure persisting after birth about the joints and at points where tendons exerting maximal traction attach themselves directly to the bone. At such points the osseous end of the tendon, which is embryologically a portion of the bone and not of the muscle,

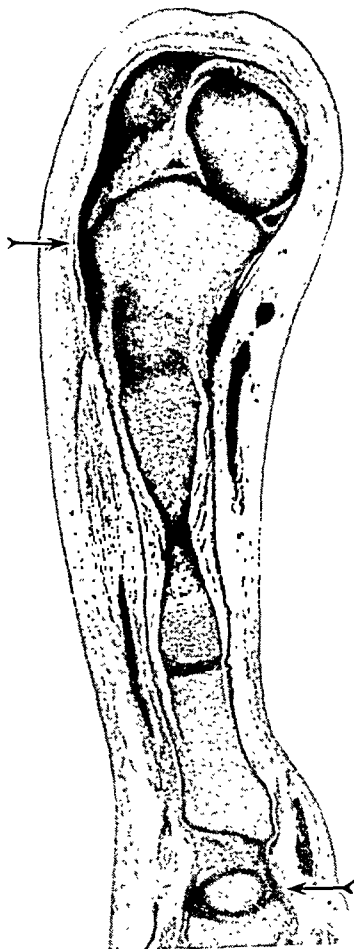


Fig. 6.—The persistance of precartilaginous connective tissue (blastema) at the ends of tendons attaching directly to bone, in the embryo, after the skeleton has been preformed in cartilage. The osseous ends of the quadriceps and achilles tendons have been indicated by arrows.

aids in the formation of a normal bony protuberance and produces both cartilage and bone through differential steps in this precartilaginous connective tissue (figs. 6 and 7). In and about normal joints also, where the articular structures are embryologically a product of the same precartilaginous tissue, developmental steps involving a transition from connective tissue to cartilage to bone may be found throughout life. usually at the point of reflexion of the joint capsule and even in the

synovia proper where chondro-osseous bodies may develop (osteochondromatosis), indicating that the embryonic tissue here is closely allied to that in the tendons.

It is important to realize, therefore, that this primary periosteal chondrosarcoma is not derived from cartilage or misplaced tissue at the



Fig. 7.—Precartilaginous connective tissue embedded in the normal tendon, giving rise to cartilage and ossification at the site of the tendinous attachment of the quadriceps to the tibial tuberosity. (The specimen was removed from a young dog.)

epiphyseal line which since the time of Virchow has been the stereotyped explanation for tumors of the bone containing cartilage. It is instead a tumor of precartilaginous connective tissue and as such it is

most frequently associated with tissue of that type which persists normally at points of tendinous attachments to bone and is closely related to benign growths known as exostoses and central chondromas derived from similar tissue, which of themselves may give rise to sarcoma of this type through secondary malignant change. The fact that all of these growths are microscopically variations of the same combination of connective tissue, cartilage and bone bears out the fact that a single fundamental histogenetic process underlies this entire range of pathologic changes.

The clinical features of primary chondrosarcoma corroborate this histogenetic analysis. This sarcoma usually involves the region of the knee or shoulder and is particularly frequent at the adductor tubercle of the femur which forms the insertion of the adductor magnus and at the tibial tuberosity where the quadriceps extensor is inserted and at the greater tuberosity of the humerus where the supraspinatus muscles are anchored. These sites of tuberosity formation are, as Leriche and Policard¹⁴ pointed out, anatomically peculiar, and as Kollicker¹⁵ originally observed, harbor a distinctive form of chondrogenesis (fig. 7). The youthful age of the patient, who is usually between 15 and 20 years, the brief duration of symptoms, averaging less than six months, and the rapidly fatal course terminating in most instances within fourteen months after treatment, emphasize the extremely primitive character of the tissue of origin.

This type of chondrosarcoma is given its clinical individuality not only by its localization near tendons, its age distribution and its acute course, but also by its roentgenologic features. It is one of the few types of lesions of the bone that produce a periosteal reaction and a soft part shadow without noticeable effect in the early stages on either the cortex or the medulla of the bone. This is more truly a periosteal form of osteogenic sarcoma than is the sclerosing form of sarcoma usually referred to by this appellation, and is distinguished from the sclerosing type by the more shaggy and plentiful periosteal new bone and the clouding of the marrow cavity produced by the latter. Palpation in conjunction with the x-ray picture also aids in the distinction, since the primary chondrosarcoma of the bone produces a firm rubbery tumor, which to the examining hand presents a larger bulk than the x-ray film would seem to indicate.

Despite these diagnostic features of the neoplasm, the primary form of chondrosarcoma is practically never distinguished by clinicians as

14. Leriche, R., and Policard, A.: *Physiology of Bone*, St. Louis, C. V. Mosby Company, 1928.

15. Kollicker, A.: *Manual of Human Histology*, London, Sydenham Society, 1853-1854, vol. 1, p. 251.

an individual type. Even when operation discloses the characteristic lobulated, bluish-white and translucent nature of the chondral mass, and microscopic examination reveals the curious combination of dense connective tissue, myxoma, fetal cartilage and lobules of pleomorphic chondral cells fringed with new bone, this singular form of periosteal sarcoma is rarely identified. Instead, it is usually classed rather loosely with a general group of cartilaginous tumors in which the border line between benignancy and malignancy is not accurately drawn, or it is placed in the general group of osteogenic sarcoma without further qualification.

A clear description of this primary form of periosteal chondrosarcoma which gives full cognizance to the precartilaginous origin of this growth, its relationship to the tendons and to the prognosis and implications for therapy cannot be obtained from a perusal of the medical literature. Yet it constitutes over one eighth of all malignant lesions of the bone in a series of over 1,700 benign and malignant tumors of the bone on file in this laboratory.

While in the secondary form of these tumors, cures by amputation or radical operation plus radium implantation are not rare, there are only two instances among eighty-four cases of primary periosteal sarcoma in which a permanent five year cure has been established. This emphasizes one of the major reasons for separating this group of tumors into a distinct class. For while the outlook in these cases is gloomy, the percentage of possible cures among the other types of osteogenic sarcoma is immediately raised; among some of these groups nearly one case in three offers an opportunity for successful treatment.

Despite the fatality of the lesion, which undoubtedly is inherent in the primitive phase of osteogenesis responsible for this tumor, unfamiliarity with the clinical and roentgenologic features probably has played an important rôle in the therapeutic failures. In the roentgenogram the early lesion is practically invisible because the chondral mass in the soft part casts little or no shadow, and the bone proper is not disturbed. The changes that are visible in the periosteum may be easily overlooked or erroneously attributed to periostitis. Usually it is not until osseous destruction due to invasion of the tumor splits the cortex and enters the marrow cavity that the nature of the growth is realized, and by this time the auspicious moment for intervention has been passed.

When the tumor involves the extremities, an early amputation undoubtedly is of greatest benefit, but it must also be borne in mind that radiotherapy, which is effective in secondary chondrosarcoma, in which cures are by no means rare, is worthy of trial. In one of the two cases in this series in which cure was obtained by amputation, treatment with radium packs preceded the amputation.

While the details of the clinical and the pathologic picture are not discussed here because they have been brought out in a preceding paper, a typical case report is given with illustrations. This report emphasizes a triad of findings on which a delineation of this entity rests: first, the features in the history of an acute course of trauma, pain, tumor and dysfunction in a patient under 30 years of age; second, the findings on examination of a tumor which is rubbery to palpation and larger than the translucent periosteal shadow in the roentgenogram seems to indicate (fig. 8), and third, a microscopic picture in which there is a characteristic transition from embryonic connective tissue to myxoma

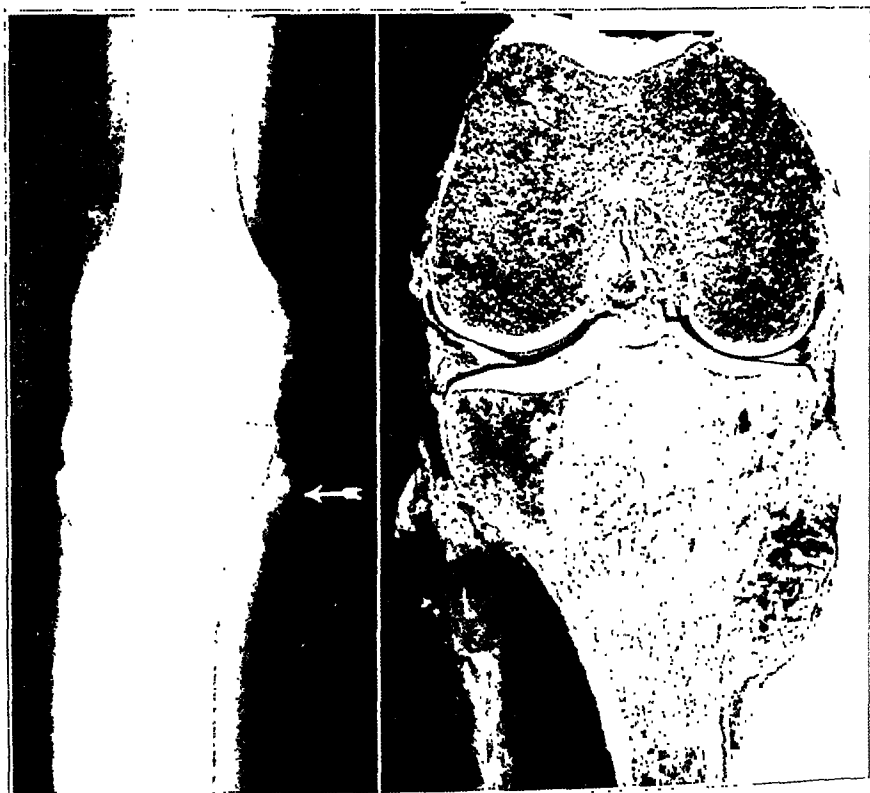


Fig. 8 (P. N. 42352).—Comparison of the roentgenogram and gross specimen of a primary chondrosarcoma occurring in a white youth, aged 20, five months after a trauma. The roentgenogram shows a small translucent periosteal tumor at the medial side of the tibial tuberosity. The longitudinal section of the gross specimen shows more definitely the size and locality of the periosteal growth, which is only faintly discernible in the x-ray film.

to cartilage to bone in which bizarre forms of fetal and adult cartilage predominate.

CASE 1 (P. N. 37930).—*Primary chondromyxosarcoma.*

History.—A white youth, aged 18, complained of pain in the lower end of the right femur of seven weeks' duration. The trouble began with an injury, which after subsiding, was followed two weeks later by severe pain. The pain was a dull ache that kept him awake at night and was relieved only by rest of the leg, when

sitting or lying down. The patient was compelled to use first a cane and then crutches because of the pain when walking.

Examination.—Physical examination gave negative results except for the region of the right knee. There was fulness over the internal condyle of the femur, and the swelling was firm and rubbery to palpation. Roentgen examination was first made sixteen days after injury, and gave essentially negative results. The other roentgenograms made five and seven weeks after injury showed a cloudy periosteal shadow about 1 inch above the internal condyle of the femur in the region of the adductor tubercle. The cortical and medullary bone beneath were essentially normal in the anteroposterior view, but in the lateral view in the

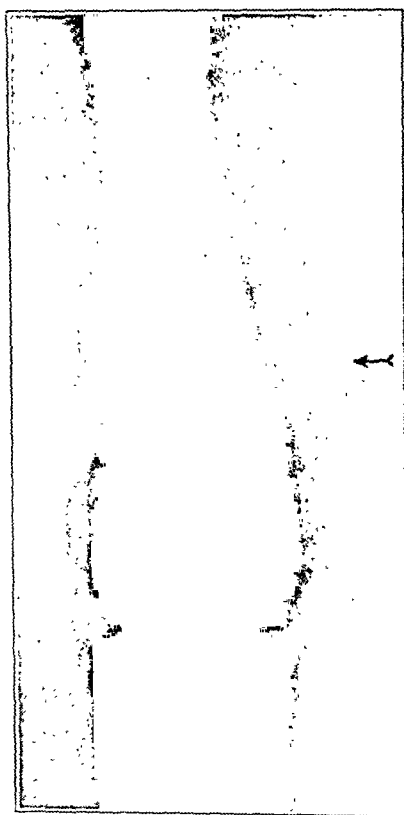


Fig. 9 (P. N. 37930, case 1).—The translucent periosteal shadow typical of primary chondrosarcoma is shown in the lower end of the femur at the site of the adductor tubercle.

popliteal region there was a small area of osseous destruction affecting only the cortex (fig. 9).

Clinical Course.—The patient received deep roentgen therapy six weeks after injury. The pain was somewhat relieved and the swelling slightly less. Eight weeks after injury an amputation at the mid thigh was performed. The patient went home and gained weight rapidly, but about eight months later there were neuralgic pains in the chest followed by a mass beneath the sternum and pleural effusion. The patient died one year after amputation had been performed.

Microscopic Report.—The section (fig. 10) showed a tumor composed of cartilage cells mainly of the adult cartilage type. The septums extending into the

chondral lobules were of a dense fibrous tissue which was actively proliferating. The cartilage cells within their capsules were undergoing all types of pleomorphism and degeneration. There were occasional myxomatous areas and slight amounts of ossification. A few calcareous areas were present.

Comment.—The duration of the disease was fourteen months with symptoms of two months and a postoperative life of one year. The tumor was primary in a



Fig. 10 (P. N. 37930).—Photomicrograph showing pleomorphic cartilage cells enclosed in lobules that simulate a benign chondroma, but the strands of proliferating embryonic connective tissue and calcification bear evidence of the malignant nature of the tumor.

young adult following an injury. Apparently neither roentgen treatments nor amputation influenced the ultimate result. Two significant features in this case are the negative roentgen findings immediately after the injury, relating the onset of this neoplasm definitely to the preceding trauma, and the complete relief from

symptoms afforded for eight months by the amputation, before the clinical manifestations of the pulmonary metastases appeared.

SECONDARY CHONDROMYXOSARCOMA

Chondromyxosarcoma is fundamentally related to a precartilaginous connective tissue, which may be found under a variety of conditions persisting periarticularly and about tendinous and ligamentous attach-



Fig. 11 (P. N. 42142).—Roentgenogram of a benign osteochondroma or exostosis. The pedicle or base of the outgrowth is formed by normal bone, continuous with the underlying shaft of the tibia. The cartilaginous cap is distinctly outlined by a rim of calcareous material.

ments. This primitive connective tissue, which has the power to form both cartilage and bone, gives rise to numerous benign tumors of the osteochondromatous and chondromatous types. Most of these benign growths are exostoses which represent an exaggerated normal bony protuberance (figs. 11 and 12). In such an exaggerated protuberance, part of which is proliferated in the tendon as cartilage and part of which is formed by a bulging of normal bone beneath, a malunion between

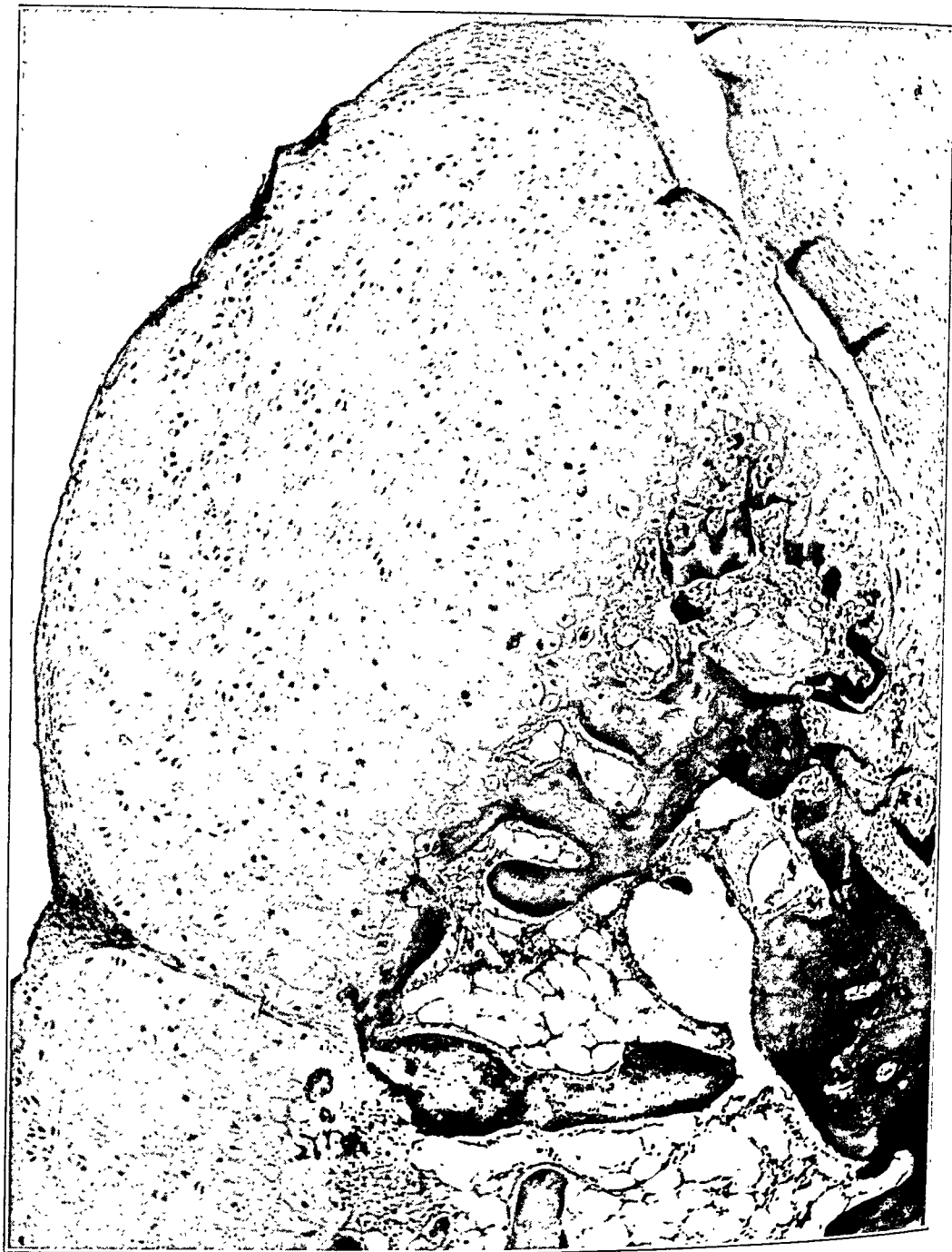


Fig. 12 (P. N. 42142).—Photomicrograph of a benign osteochondroma or exostosis. In the one microscopic field, there is shown three distinct zones, the first, a narrow rim of connective tissue (of the precartilaginous type) at the outer margin, dipping into the tumor to form lobules; second, a middle area of cartilage, which is gradually undergoing calcification, and third, normal cancellous bone enclosing a small amount of fatty bone marrow.

fibrous tissue of the tendon and the adjoining periosteum allows an overproduction of both chondral and osseous structures.¹⁶ In another type of related growth, the central chondromas, the localization of the tumor in the small bones of the hands and feet and about the ribs and sternum where joint surfaces in the body are most numerous suggests that the neoplasm begins as an aberrant articulation. Pathologically, strands of precartilaginous tissue in these neoplasms identical with a type that traverses the bones at right angles to their axis to form joints in the embryo supports this interpretation. In all of these benign tumors, whether of the exostoses or chondroma type, the persistence of



Fig. 13 (P. N. 26917).—Roentgenogram showing a primary chondrosarcoma arising at a site similar to that of the exostosis shown in figure 11. Note the translucent character of the periosteal growth and the mottled areas in the tibia beneath.

functioning connective tissue of this embryonic, precartilaginous type makes possible the origin of secondary chondrosarcoma which becomes superimposed on the original benign growth.

In general, these lesions are different from primary chondrosarcoma, although on the basis of the microscopic section the distinction between the two forms cannot often be made. In contrast to the adolescent age of the patients with primary chondrosarcoma, those afflicted with the secondary form are most often over 30. Instead of a brief acute

16. The formation of these benign tumors is fully discussed in another article (footnote 10).

symptomatology, the history usually given is a vague rheumatic complaint, with weakness or deformity in the affected member persisting over a period of many years (from five to twenty-five) and complicated in recent months by more severe symptoms of pain and swelling.

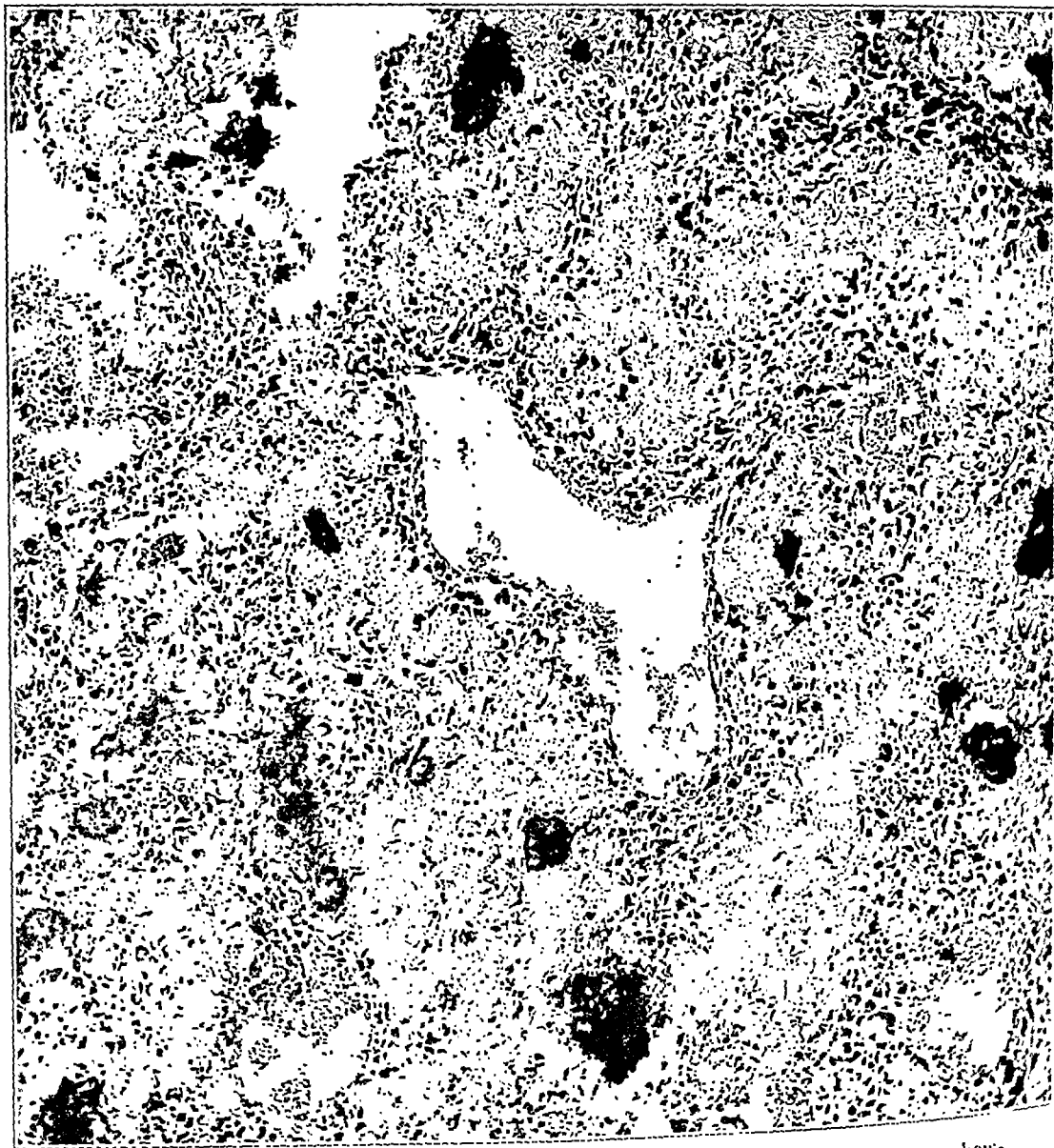


Fig. 14 (P. N. 32909).—Photomicrograph of a primary chondrosarcoma showing the disorderly arrangement of connective tissue, cartilage and bone, typical of this malignant new growth. Compare with figure 12.

The roentgenologic findings are far more varied than those in primary chondrosarcoma and depend on the nature of the preceding benign lesion and the duration of the malignant change. If a single or one of multiple exostoses is the seat of the sarcomatous growth, the earliest change is periosteal. A haziness in the outer margin of the preexisting

benign growth rapidly extends downward producing a granulating and spotted destruction in the medullary cavity of the bone beneath. Even in late cases in which the benign bony outgrowth has been completely destroyed, the widened metaphyseal region typical of both single and multiple exostoses gives evidence of the secondary nature of the sarcoma (figs. 11, 12, 13, 14 and 15).

When a central chondroma is the site of the malignant change, the multilocular structure of the original tumor will partially persist and the expansion of the bone due to the first growth is usually evident. Sometimes the chondromatous lesions are multiple, and those uninvolved by



Fig. 15 (P. N. 44148).—Transformation of the type of lesion shown at figures 11 and 12 into the type shown at figures 13 and 14. The primitive connective tissue and chondral elements in the exostosis which is clearly visible in *A* are proliferating, giving rise to the infiltrative, malignant lesion shown in *B*. *A* and *B* are roentgenograms of identical lesions in the same patient taken six weeks apart. This secondary chondrosarcoma shows a degree of malignancy intermediate between that of the benign exostosis and that of primary chondrosarcoma.

sarcoma give the key to the original status. If Paget's osteitis deformans has been the forerunner of secondary chondrosarcoma, the characteristic generalized changes in the skeleton will be present. Rarely a peculiar calcified area of cartilage occupying a condyle or a normal bony protuberance will remain quiescent from birth or cause only vague rheumatic complaints and then without apparent provocation show the infiltrative changes of secondary chondrosarcoma (figs. 20, 21, 22 and 23).

The clinical course and the response to the various methods of treatment are typical in secondary chondrosarcoma. Slow growth to a tremendous size is the rule in the untreated cases, and many of the huge chondromas of the older authors belong to this category. These tumors tend to recur promptly after incomplete surgical measures and are easily transplanted into the wound, but metastases are slow to develop so that many of the patients survive unsuccessful operation from three to five years. Of the modes of therapy, partial excision is the most disastrous. Curetting followed by extensive thermal cauterization is rarely successful. The best results are achieved by amputation or radical excision followed by radium therapy.¹⁷

From the standpoint of the pathologist, these tumors present an extremely difficult diagnostic problem. While the protracted history and the adult age of the patient and the bone-destructive character of the lesion superimposed on a previous abnormality, as shown in the roentgenogram, make the distinction from primary chondrosarcoma perfectly definite, under the microscope there are no such reliable guides. As a rule, the sections in secondary chondrosarcoma are predominated by myxoma and necrotic cartilage, whereas in primary chondrosarcoma there is a greater mixture of cells with a transition through all phases of osteogenesis—from connective tissue to cartilage to bone with pleomorphic forms of cartilage predominating.

The entire problem, however, is far more difficult when an attempt is made to distinguish microscopically between secondary chondrosarcoma and the benign chondromas. In many instances the distinction by means of the microscope is impossible, but fortunately there are other criteria. Foremost is the matter of localization. Cartilaginous tumors of the small bones of the hands and feet (excluding the os calcis) may be regarded as benign regardless of the microscopic pathologic changes. On the other hand, all central tumors of the long bones, sternum, spine and pelvis, composed predominantly of cartilage particularly those giving evidence of recent increase in size or intensity of symptoms, must be looked on as potentially malignant.¹⁸ Especially

17. Dr. W. Sampson Handley of London, in a personal communication (Feb. 1, 1931), set forth his experience with radium therapy in the treatment for sarcoma of this chondral type. He exposes the tumor and chisels away the main mass, after which large doses of radium are buried for a short time in the wound (500 mg. for twenty-four hours). Of five patients thus treated, one is well for three years and two had recurrences after three years of active life and freedom from pain. These are good results in view of the fact that after the usual unsuccessful operation this group of tumors recur very promptly in the wound. The sloughing of tissues with such intensive irradiation he believes is unavoidable.

18. Wolbach has followed the same rule laid down in this paper. Independently of the results in this laboratory, it has been Wolbach's experience in Boston that cartilaginous tumors of the large bones, regardless of their pathologic process, must be considered potentially malignant.

when recurrence in the growth in one of the long bones has followed incomplete surgical removal, the lesion must be regarded as sarcomatous from the clinical point of view.

In this matter of localization of the growth there is a striking histologic paradox. In the lesions of the small bones, although the clinical course is distinctly benign, microscopic examination usually reveals a mixture of myxomatous fetal cartilage and new bone indistinguishable from the chondromyxosarcoma of the primary type. On the other hand, in confirmed cases of secondary chondrosarcoma of the large bones terminating in death by metastasis, the histology of the

TABLE 1.—*Comparison of Clinical and Pathologic Features of Primary and Secondary Chondrosarcoma*

	Primary*	Secondary*
Number of cases.....	84	80
Origin.....	Junction of tendon and bone	Previous benign skeletal tumors
Sex.....	Males, 2:1	Males, 2:1
Race.....	Blacks, 15%	Blacks, 6%
Most frequent ages.....	14 to 21 yrs.	30 to 50 yrs.
Favorite sites.....	About the knee, upper part of humerus	Shoulder and pelvic girdle, knee and heel
Duration of symptoms.....	3 to 5 mos.	2 to 25 yrs.
Usual symptoms.....	Pain, tumor, tenderness	Pain, tumor, tenderness
Trauma.....	22%	22%
Pathologic fracture.....	None	6%
Constitutional manifestations.....	Occasional fever, leukocytosis, enlargement of regional lymph nodes; secondary anemia	Systemic reactions rare, secondary anemia
Roentgenograms.....	Periosteal translucent tumor, slight new bone	Central osseous destruction with periosteal reaction
Microscopic features.....	Pleomorphic forms of cartilage predominate	Myxoma and fetal cartilage predominate
Percentage of 5 yr. cures.....	5%	24%

* For detailed tabulation of these cases see Geschickter (footnote 10).

local growth which has been the seat of sarcomatous change is often indistinguishable from a benign chondroma.

- Besides this matter of localization and of recurrence, the distinction between secondary chondrosarcoma and benign cartilaginous growth is materially aided by a familiarity with the clinical, roentgenologic and pathologic features of benign exostoses and central chondromas. As long as an exostosis in the roentgenogram has a pedicle of normal osseous tissues and a cartilaginous cap distinctly outlined by calcification, malignant change may be excluded. When under the microscope the transition from the overlying fibrous membrane through adult calcified cartilage to normal underlying bone can be visualized through two or three successive fields of low powered magnification, the lesion is distinctly benign (figs. 11 and 12). Also the histologic appearance

of the membranous capsule of the tumor as it dips into the cartilaginous portions of growth, dividing it into lobules, gives evidence of a quiescent state, whereas in sarcoma the connective tissue strands always show signs of active proliferation.

In the benign central chondromas a translucent central area of osseous destruction, traversed by interlacing demarcations and surrounded by a definite bone shell, distinguishes these lesions in the roent-

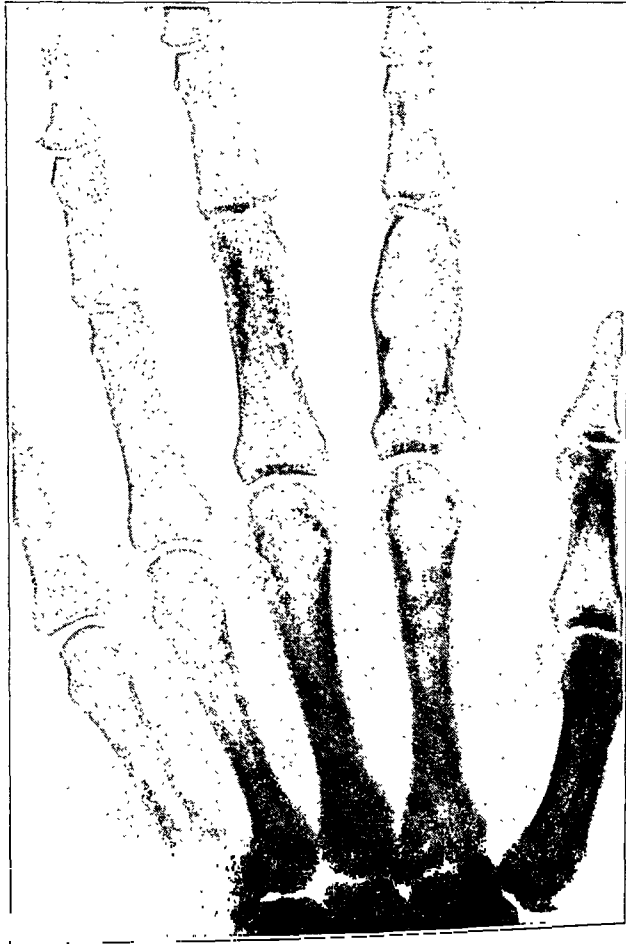


Fig. 16 (P. N. 28464).—A benign central chondroma occurring in a typical location (a phalanx of the finger). The central character of the lesion, its clearly demarcated bone shell and the finely multiloculated or "cotton-wool" appearance of the rarefied area are shown.

genogram from those growths in which malignant change has occurred and wherein there is usually a hazy and invasive periosteal growth beyond the bone shell, in addition to a granular and spotty change within the central area. Under the microscope the benign chondromas are usually composed of fairly uniform adult cartilage which closely resembles the normal chondral type, and the fibrous septums that lobulate the tumor are in a quiescent and hyalinized state (figs. 16 and 17).

From the practical standpoint of treatment, the important considerations in dealing with lesions in the cartilaginous group are:

1. Cartilaginous lesions of the small bones of the hands and feet, excluding the os calcis, regardless of their histology may be treated as

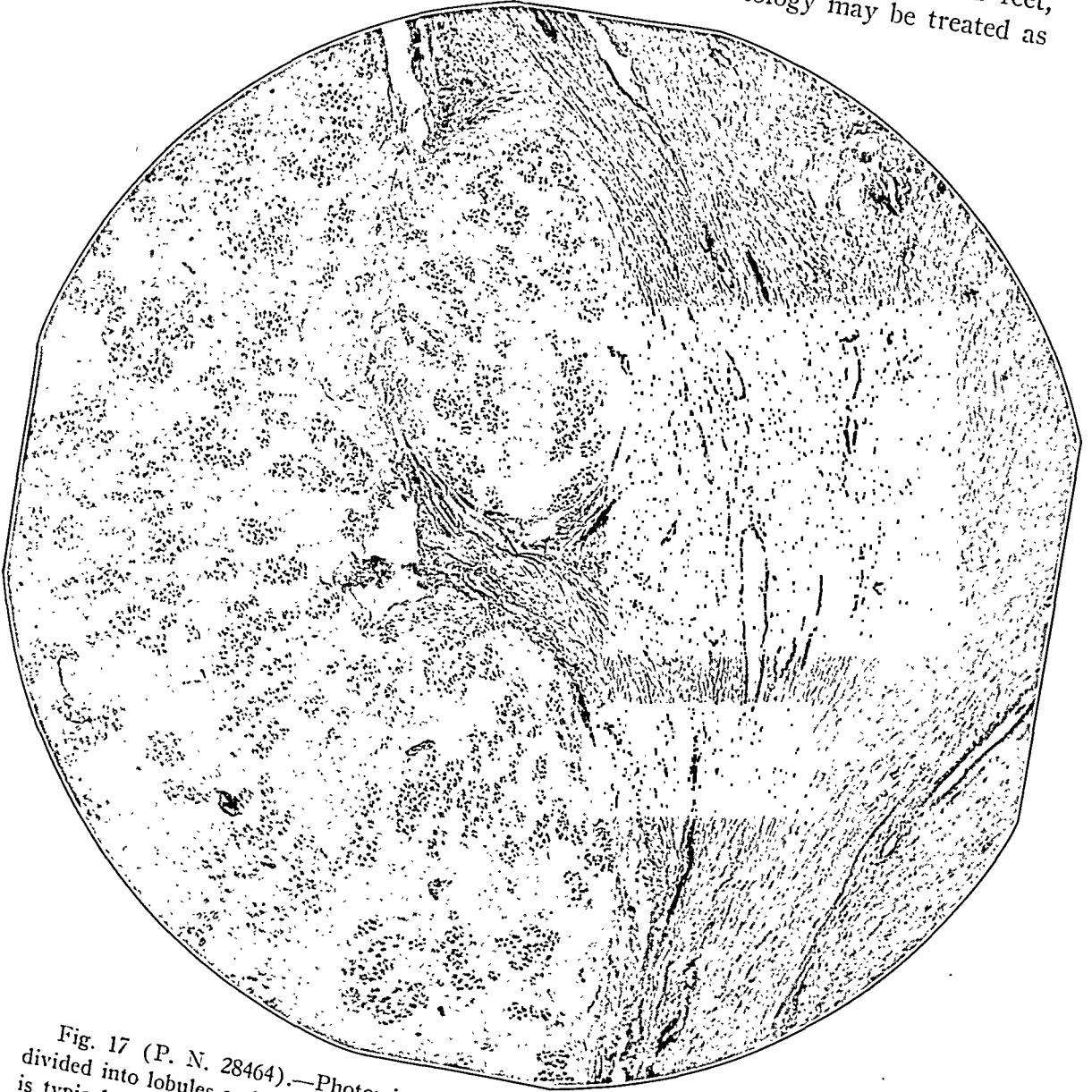


Fig. 17 (P. N. 28464).—Photomicrograph showing the typical adult cartilage divided into lobules and the hyalinized state of the connective tissue stroma, which is typical for these benign lesions.

benign and extirpated by curettage followed by chemical or thermal cauterization.

2. All cartilaginous lesions of the large or long bones in adults in which there is a history of mild chronic symptoms over a period of

many years followed recently by an increase in size and in severity of symptoms and in which the medullary cavity is either primarily or secondarily involved by infiltrative destruction of the bone must be looked on as clinically malignant regardless of their histology. A trial by deep roentgen therapy in adequate doses should first be made to control the growth and, if this fails, amputation or radical resection in which the knife is not allowed to encounter the area of the tumor should be carried out, followed by roentgen or radium therapy.

3. A primary periosteal tumor with brief, acute symptoms, occurring in a patient under 30, that shows in the roentgenogram little or no involvement of medullary or cortical bone and in which there is no visible pedicle or base formed by osseous tissue in relation to the translucent periosteal shadow, is usually a primary chondrosarcoma. The part should be put at immediate rest, deep roentgen therapy given and the x-ray films sent for consultation to one competent to judge. If the diagnosis is confirmed, an amputation or radical resection well above the lesion should be performed. If the lesion is in the upper end of the femur or otherwise inaccessible, radical excision with the cautery followed by radium implantation should be tried.

The points brought out in the preceding discussion are reemphasized in the case reports and illustrations that follow.

CASE 2 (P. N. 28246).—*Secondary chondromyxosarcoma arising in hereditary deforming chondrodysplasia.*

History.—A white woman, aged 41, had had skeletal abnormalities since birth and gave a family history that showed this to be hereditary. The father had multiple exostoses in both tibiae. An uncle on the father's side was similarly affected. A sister of the patient, aged 32, had a bony growth on one tibia, and a brother, aged 35, had similar growths in both legs and arms and on the right pelvic brim, all of which had been discovered at the age of 10. The patient was born with extra digits on the feet, one next to the large toe on the left foot, and one on the middle toe on the right foot. At the age of 3, growths were noticed on both arms. The present illness began three years before examination with pain in the back on the right side, extending toward the pelvis. The pain had become rapidly worse in the last year.

Examination.—There was a large mass in the right lumbar region which could be felt adjoining the spine, just above the pelvis. The roentgenogram showed multiple exostoses of the bones of the legs and arms and a less clearly defined tumor protruding from the transverse process of the fourth lumbar vertebra (fig. 18). This process had been partly destroyed and was capped by a cauliflower translucent growth with some calcification in its substance.

Clinical Course.—Local physicians thought that the mass contained fluid and under a diagnosis of cyst, an attempt was made to aspirate it. Later an exploratory operation was done, and a piece of tissue removed for diagnosis. The tumor gradually increased in size, and there was increased pain radiating to the right leg. The patient died two years after the operation. An autopsy was performed.

Gross Specimen.—The tumor weighed 8 Kg. and was a large lobulated mass of cartilaginous material attached to the lumbar spine. It was encapsulated by fibrous tissue, and very hemorrhagic in points. At autopsy, secondary growths were found in the liver, the right suprarenal and the lungs. There were spurs and cystic tumors of a benign character in the long bones, ribs, etc.

Microscopic Report.—The sections showed numerous cartilaginous areas (fig. 19). The cartilage cells were of the adult type and resembled the benign chondroma more than the malignant chondromyxosarcoma. But the hyaline matrix was scant and contained more cells, many of which were undergoing pleo-

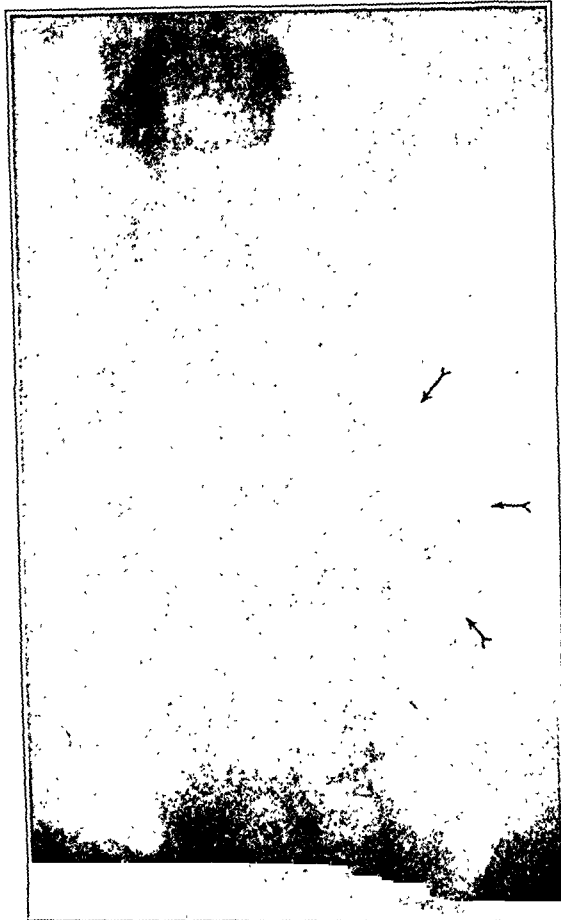


Fig. 18 (P. N. 28246, case 2).—Malignant change in an osteochondroma of the transverse process of the fourth lumbar vertebra in a white woman, aged 41, who suffered from hereditary deforming chondrodysplasia. There were multiple exostoses in the bones of the legs and arms. The sister and brother of the patient suffered from similar defects, as did an uncle on the father's side. The infiltrating character of the lesion is shown.

morphism. A few thin strands of fibromyxomatous tissue were present. The section, which was secured during the exploratory operation, was not representative of the malignant nature of the tumor.

Comment.—This is an unusual case of congenital multiple exostosis with a distinct hereditary basis. These tumors, originally benign, underwent secondary



Fig. 19 (P. N. 28246).—High power photomicrograph of the lesion shown in figure 18. Note the proliferating embryonic connective tissue strands between the lobules of cartilage. The patient died two years after the exploratory operation, with generalized metastases. An autopsy was performed.

malignant change in one area, leading to the death of the patient. If the symptoms in the spine are taken as the onset of the malignant change, the subsequent duration of life was five years.

CASE 3 (P. N. 34522).—*Secondary chondromyxosarcoma arising in a benign chondroma.*

History.—A white woman, aged 41, came under observation with bilateral lumps in the breast that were removed and diagnosed blue dome cyst and intracanalicular myxoma. She had had an old trauma twenty-eight years previously in the left knee with occasional swelling and stiffness of the left knee joint for about ten years. Some pain and limping were present for the past four years.

Roentgen Examination.—The roentgenogram (fig. 20) made previous to exploration showed increased calcification and ossification of the internal condyle of



Figs. 20-25 (P. N. 34522; case 3).—Illustrations of a case of secondary chondrosarcoma arising in a chondromatous lesion in the internal condyle of the left femur. The condition had caused symptoms for over twenty years. The patient died of metastasis ten years after the exploratory operation in spite of amputation well above the knee. This roentgenogram (fig. 20) shows the calcified lesion in the femoral condyle before the malignant properties of the tumor became manifest. The film was taken ten years before death of the patient (November, 1920).

the left femur. There are no anteroposterior views available, but the lateral views suggest a benign calcifying chondroma. Just after the operation on the breasts, the left knee was explored.

Clinical Course.—On Nov. 19, 1920, exploration showed no fluid in the knee joint and normal soft tissues. The bone was not injured. The patient returned for further treatment in January, 1924. The pain had increased in severity, and limping had been present for ten months. Roentgen examinations made on Jan. 8, 1924 (figs. 21 and 22) showed destruction of the femur at and above the condyle

just superior to the old calcified area. The destruction of the bone had extended across the medullary cavity, and there were definite periosteal shadows on both sides of the lower end of the femur with lifting of the periosteum. Amputation was performed without exploration on January 23. In 1929, nearly six years after the amputation, the patient had metastases to the frontal bone and unilateral exophthalmos (figs. 24 and 25). She died with generalized metastases in December, 1930.

Gross Specimen.—The gross specimen showed medullary invasion above the condyle of the femur. The tumor material was soft and gelatinous and definitely

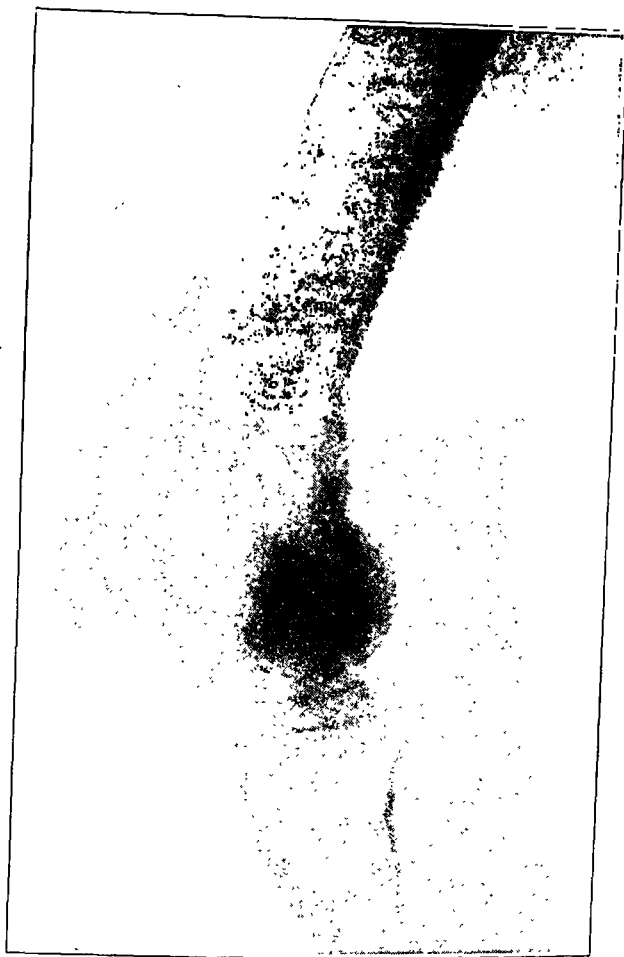


Fig. 21 (P. N. 34522).—Lateral view of the lesion shown in figure 20, three years later (January, 1924), showing the invasive and malignant character of the growth. Note the persistence of the old calcified area in the condyle.

of the consistency of chondromyxoma. The original tumor area invaded the cancellous bone of the internal condyle and apparently was not periosteal in origin (fig. 23).

Microscopic Report.—The sections showed a fibrous myxomatous tissue with some calcifications in chondral areas and a few early cartilage cells. There were some spicules of new bone. The bulk of the tumor area seemed to be made up of chondroblasts with fringes of a calcifying matrix.

Comment.—This is undoubtedly a secondary form of chondromyxosarcoma arising in a cartilaginous rest which occupied one of the condyles of the femur. Symptoms had been present for ten years at the time of the exploration and fourteen years at the time of amputation. The malignant change had been present at least ten months before amputation and possibly for four years at the time of the first exploration. Seven years after amputation, the patient died with metastases to other bones.

CASE 4 (P. N. 39952).—*Secondary chondromyxosarcoma arising in a benign exostosis.*



Fig. 22 (P. N. 34522).—Anteroposterior view taken at the same time as figure 21.

History.—A colored youth, aged 18, gave a history of injury two and one-half years previously. Following this there was a definite lump in the left thigh which steadily increased in size. The patient was kept under observation, and the mass grew steadily and was thought to be a periostitis or ossifying myositis.

Examination.—The results of the general physical examination were negative. On the lower third of the left femur there was a mass the size of a grapefruit which was firm to palpation. A second mass opposite the larger one was palpable in the external region of the thigh. There was no enlargement of the regional lymph nodes. Function of the leg was not impaired (figs. 26, 27 and 28). Roent-



Fig. 23 (P. N. 34522).—Portion of the specimen from the leg amputated in January, 1924. The waxy, hyalinized mass represents the malignant portion, the spongy, honey-combed area in the condyle the primary portion of the growth.



Fig. 24 (P. N. 34522).—Exophthalmos caused by metastases to the frontal bone. The photograph was taken in November, 1927.



Fig. 25 (P. N. 34522).—Large area of bone destruction in the left frontal bone produced by metastases (November, 1927). The patient died with generalized skeletal metastases in October, 1930.



Figs. 26-30 (P. N. 39952; case 4).—Illustrations showing malignant change in a benign exostosis in a colored boy, aged 18, following an injury two and one-half years previously. This photograph (fig. 26) of the patient, taken in June, 1929, shows the bony swelling at the site of the adductor tubercle, eighteen months after the onset of malignant change.

gen examination showed a bony mass attached to the lower shaft of the femur projecting into the soft parts. Surrounding this bony tumor, which had the appearance of an exostosis, was a large cloudy mass with a few radiating lines of new bone.

Clinical Course.—Because of the rapid growth, malignancy was suspected, and amputation was performed. This was in July, 1929, and the patient has had no recurrence since leaving the hospital (July, 1931).

Gross Specimen.—The gross specimen showed (fig. 29) a definite exostosis of compact and cancellous bone about 2 inches in length extending outward from

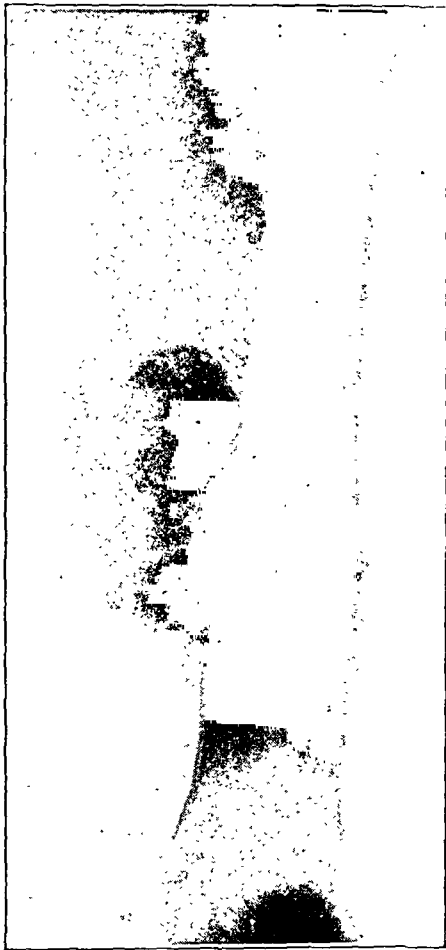


Figure 27

Fig. 27 (P. N. 39952).—Roentgenogram taken in December, 1929, showing the early signs of malignant change in the exostosis. Note the fracture through the benign portion of the lesion and the sarcomatous periosteal reaction on the opposite side of the femur.



Figure 28

Fig. 28 (P. N. 39952).—Roentgenogram showing the progress of the sarcomatous growth in June, 1929.

the lower shaft of the femur. There was a large cartilaginous cap on the exostosis which was undergoing secondary malignant change. Large lobules of fibrocartilaginous material had proliferated from the tissue immediately over the exostosis. These lobules surrounded the entire lower half of the femur, but did not invade the cortex or medullary cavity of the bone.

Microscopic Report.—Microscopic sections showed trabeculae of laminated and newly formed bone, surrounded by fibrous tissue and myxomatous areas. Many fetal cartilage cells were present in the myxomatous tissue. Here and there were a few giant cells. A malignant ossifying fibrous tissue was present (fig. 30).

Comment.—This is an unquestionable case of sarcoma arising secondarily in a benign exostosis of the femur which had probably been present since birth. The cartilaginous cap and the soft parts immediately over the exostosis are the seat of



Fig. 29 (P. N. 39952).—Photograph of the specimen from the amputation performed in July, 1929. The osseous pedicle of the original exostosis is clearly shown surmounted by a cystic cartilaginous cap. The huge sarcomatous mass is surrounding this primary lesion.

malignant change. Although it is too early to judge the ultimate results, a definite hope is entertained for the life of this patient.

CASE 5 (P. N. 29616).—*Secondary chondromyxosarcoma arising in Paget's disease of the bone.*

History.—A white man, aged 64, whose family and past histories were unimportant, four months previously noticed pain in the right leg just below the

knee. Despite various palliative treatments, the pain grew worse and extended along the tibia causing him to limp for a month before admission. There was a history of trauma at the onset of the symptoms.

Examination.—On Feb. 11, 1922, the general examination gave essentially negative results save for the affected limb. There was slight bowing of the upper half of the right tibia, and on palpation the bone became larger at the middle third

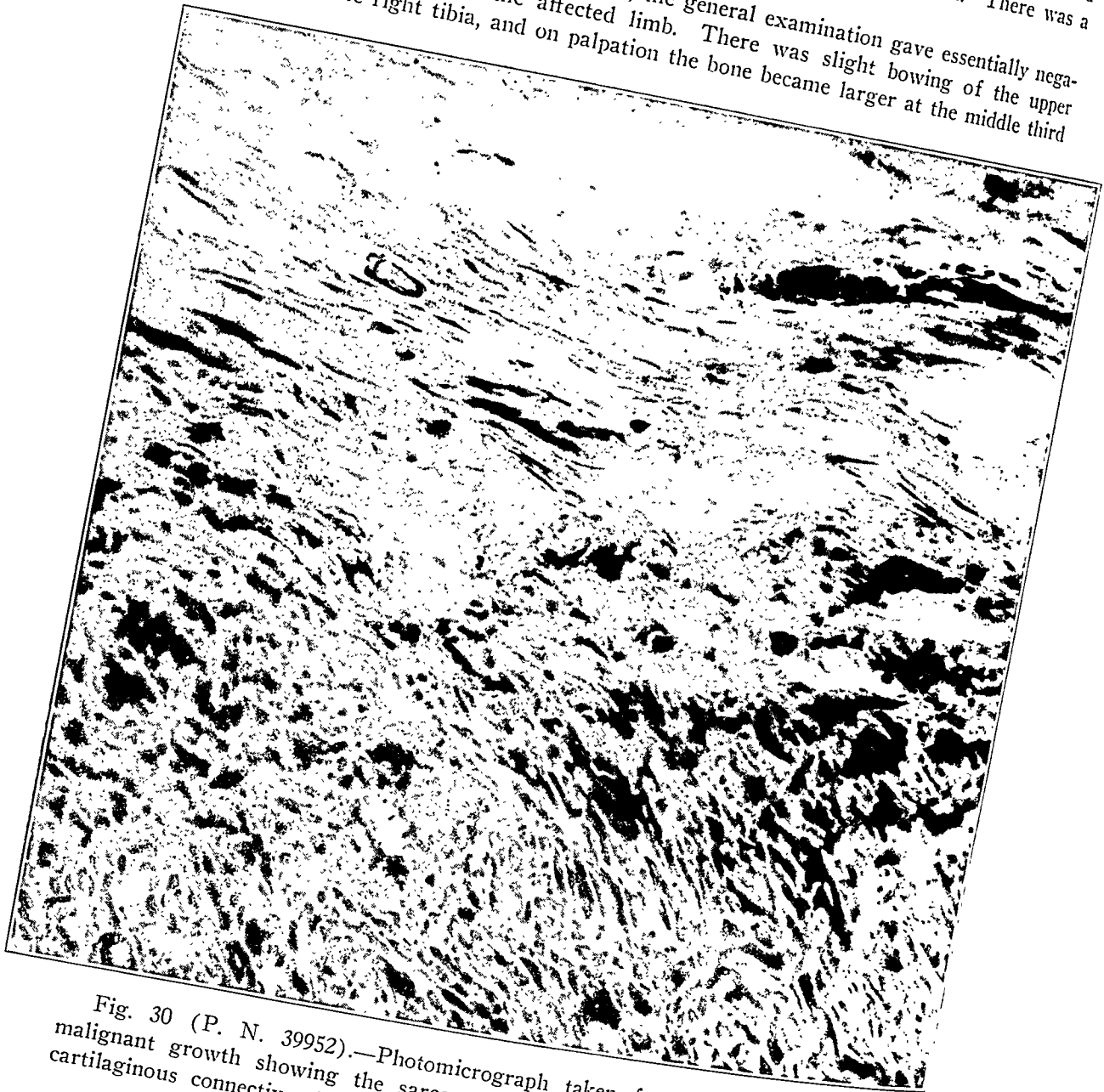


Fig. 30 (P. N. 39952).—Photomicrograph taken from the margin of the malignant growth showing the sarcomatous proliferation of the primitive pre-cartilaginous connective tissue.

and gradually expanded toward the knee joint. There was slight limitation of motion in both flexion and extension of the knee, with some swelling of leg and foot. There were 9,050 white blood cells and 85 per cent hemoglobin, and urine was negative for Bence-Jones bodies. Roentgen examination of the right tibia showed marked thickening and increased density at the head of the bone and the upper two thirds of the cortex (fig. 31). The medullary canal was encroached

on by this increased density in the upper third of the tibia. The right fibula and knee joint appeared normal. Roentgen examination of the pelvis demonstrated increased density of the bone with some irregularity of the periosteum of both the rami of the right and left pubic and ischial bones (fig. 32). Both hip joints appeared normal. The clinical impression was noted at this time as low grade chronic multiple osteomyelitis with periostitis.

Clinical Course.—The patient symptomatically improved with rest in bed, checking of the foci of infection and change of diet, and again became ambulatory. Further roentgenograms were taken which showed increased changes in the tibia,



Figs. 31-34 (P. N. 29616, case 5).—Secondary malignant change in a white man, aged 64, who suffered from Paget's osteitis deformans. This figure (fig. 31) and also figure 32 show an involvement of the right pelvis and right tibia by typical Paget's osteitis. Malignant change at this time was not suspected. Six months later there was increased pain and swelling in the right leg, pointing to malignant change, and amputation was performed.

largely bone-destructive in type. The pain and swelling of the right leg increased. At this time, Dr. Bloodgood suggested the possibility of sarcoma arising in an old area of Paget's disease. Roentgen therapy was instituted without benefit at the Memorial Hospital in New York. Amputation of the right leg through the mid-thigh region was performed on August 18 by Dr. Edgar B. Grier (fig. 33). Soon after, suggestive symptoms of metastasis to the spine developed, and the patient died four weeks after operation, in September, 1922.

Microscopic Report.—The microscopic picture was that of chondrosarcoma (fig. 34). Early connective tissue giving rise to fetal and adult cartilage with areas of calcification and ossification was present.

Comment.—This is a case of chondrosarcoma arising secondarily in a bone, the seat of Paget's disease. At the first examination the x-ray picture was felt to be that of a multiple nonsuppurative osteomyelitis, and only after further bony changes in the tibia took place did the possibility of malignancy present itself.

CHONDROBLASTIC SARCOMA

While primary and secondary chondrosarcomas arise from the more primitive precartilaginous connective tissue persisting in and about the



Fig. 32.—Roentgenogram showing increased density of the bone with some irregularity of the periosteum of both rami of the right and left pubic and ischial bones.

bone, there is another chondral form of tumor of the bone which arises from the cartilage cells of the epiphyseal line in adolescence. This type of chondrosarcoma involving the epiphyseal chondroblast is one of the more malignant forms of osteogenic tumor, but fortunately is infrequent. Although microscopic illustration of this new growth may be found in Borst's¹⁹ text under the category of chondrosarcoma and in Kolodny's¹² work under osteogenic sarcoma, that this tumor has not yet been clearly recognized as a histogenetically distinct entity is evidenced by the fact that Borst¹⁹ described certain forms of this lesion

19. Borst, Max: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902.

under endotheliomas; Kolodny, following the lead of Ewing,¹³ has labeled one of these cases a "metastasizing giant cell tumor," and Codman²⁰ called a group of these lesions epiphyseal chondromatous giant cell tumors. Not the least serious of the modern mistakes in regard to this neoplasm is to diagnose it as a benign giant cell tumor. An analysis, therefore, that will set this form of sarcoma on its proper basis and delineate its separate clinical and pathologic features should prove of definite value in avoiding pitfalls of diagnosis and mistakes in treatment.



Fig. 33 (P. N. 29616).—The gross specimen following amputation. The upper end of the tibia was involved by a chondrosarcoma which proliferated into the popliteal space. Note the cystic character of the tumor mass.

Clinical Features.—The age incidence, the site of the tumor and the short duration of the clinical course are the outstanding clinical features of this chondroblastic tumor. Patients about the age of puberty are chiefly affected. In a series of twenty-four cases, nineteen are in the decade of life between 10 and 20 years with the majority between the narrow age limits of 14 to 19. On the basis of age alone, therefore,

20. Codman, E. A.: Epiphyseal Chondromatous Giant Cell Tumor of the Upper End of the Humerus, *Surg., Gynec. & Obst.* 52:543, 1931.

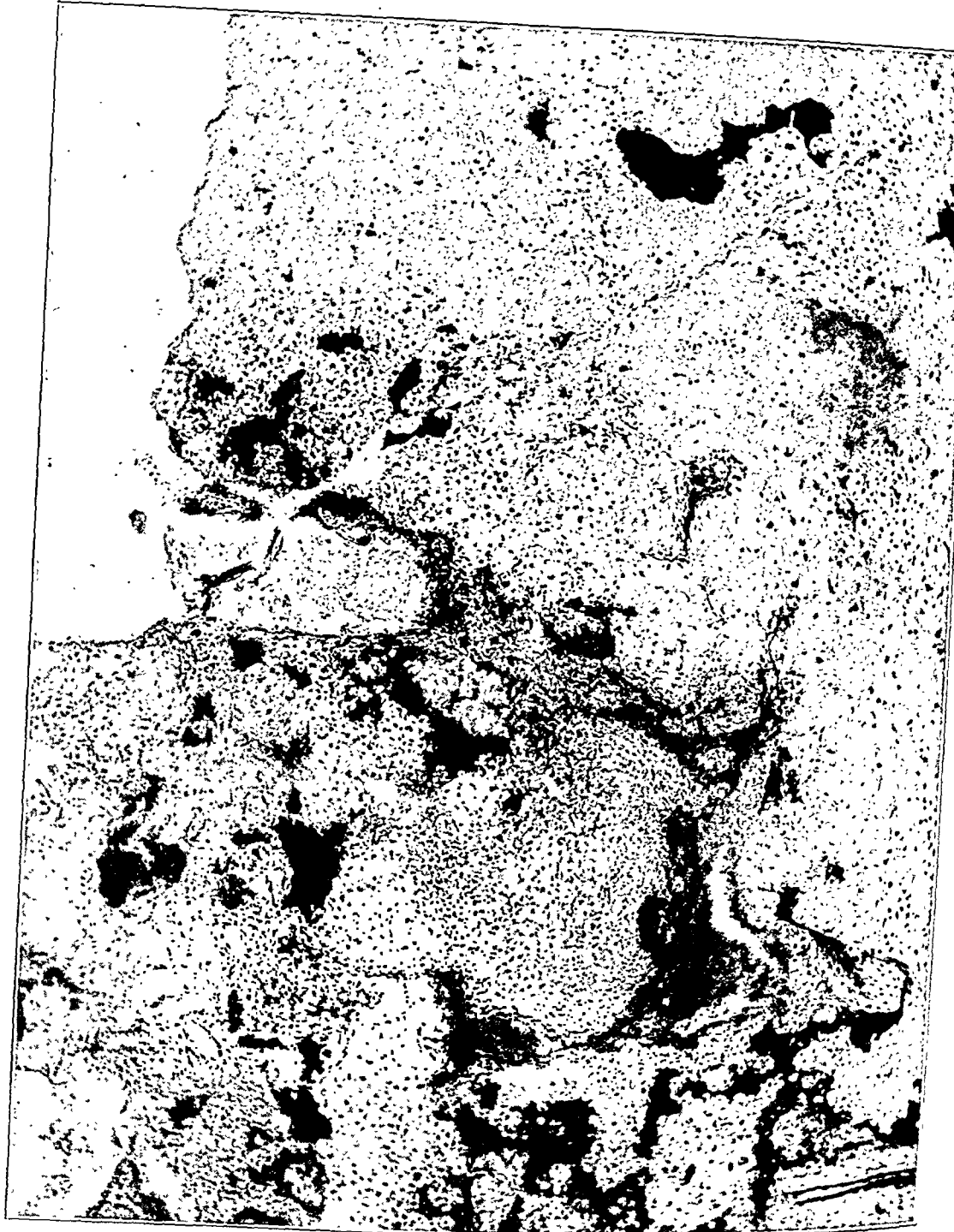


Fig. 34 (P. N. 29616).—Photomicrograph showing the admixture of early connective tissue, cartilage and ossification typical of chondromyxosarcoma.

this tumor may be linked with the process of bony growth, particularly with the bony changes occurring about the epiphyseal line, where ossification via the route of temporary calcified cartilage is taking place at the adolescent period and the epiphyseal line is undergoing ossification.

The localization of the tumors bears out this supposition. Nine of the cases of this series are in the lower end of the femur, four in the upper end of the tibia, six in the upper end of the humerus and one in the lower end of the radius. As pointed out by Poland²¹ in his work on "Traumatic Separation of the Epiphyses," it is the upper ends of the humerus and tibia and the lower ends of the femur and radius in which skeletal growth is most active. It is at these sites, when ossification is in process, that the chondroblastic forms of chondral sarcoma arise, and roentgen studies confirm the relationship of this tumor to the growth center of the bone at the epiphyseal line.

There is also a definite correlation between age and duration of symptoms in this tumor. In patients under 20 the average duration of symptoms is less than five months, while in the rare cases in which the patients are 30 years and over the duration of the disease averages over three years. The sequence and character of the clinical events in themselves, however, show no such gradation, and in this respect the history resembles the usual story of any sarcoma of bone. Trauma, pain, tenderness and tumor are reported in the order given in most cases, and dysfunction with limp or stiffness is almost a constant accompaniment when the lesion is in the weight-bearing extremity. Pathologic fracture is reported in only three instances of the series, although this is clearly a bone-destructive neoplasm (the rarity of this complication being attributable in all probability to the acuteness of the disease). Fever, leukocytosis and enlargement of the regional lymph nodes are not infrequent in this clinical entity and may be encountered in cases of the other types of sarcoma of the bone. This detracts from the diagnostic value of these findings which have frequently been stressed as peculiar to Ewing's sarcoma of the bone (Ewing,²² Connor²³), since these systemic reactions, as pointed out in a previous study (Copeland and Geschickter²⁴), are to be associated with the rapid malignant growth of the tumor resulting in early dissemination and metastasis and are not peculiar to the histologic nature of the sarcomatous growth.

21. Poland, J.: *Traumatic Separation of the Epiphyses*, London, 1898.

22. Ewing, J.: *Endothelial Myeloma of Bone*, Proc. New York Path. Soc. **24**:93, 1924.

23. Connor, C. L.: *Endothelial Myeloma*, Ewing, Arch. Surg. **12**:789 (April) 1926.

24. Copeland, M. M., and Geschickter, C. F.: *Ewing's Sarcoma*, Arch. Surg. **20**:246 (Feb.) 1930.

TABLE 2.—*Chondroblastic Sarcoma*

P. N.	Race, Sex, and Age		Location	Duration, Mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Result
44988	W	M	16	12	Pain, joint swelling	Bone rarefaction	Curettement	Proliferating chondroblasts	Amputation advised
44090	W	F	24	6	Pain, tumor	Bone rarefaction	Curettement	Proliferating chondroblasts	Unimproved
41819	W	F	40	12	Tumor	Exploration	Proliferating chondroblasts	Unimproved
40874	W	F	30	60	Pain, trauma, tumor, pathologic fracture	Periosteal roughening, bone destroyed and expanded	Curetted, irradiation, amputation	Calcification, giant cells	Dead 3 yrs. later
40872	W	M	19	4	Tumor, pain	Central rarefied area, periosteal roughening	Curetted twice, irradiation, amputation	Proliferating chondroblasts	Dead 2 yrs. later
40692	W	M	17	9	Pain, limp	Circumscribed, rarefied area	Exploration, irradiation	Proliferating chondroblasts	Pulmonary metastases
40428	W	M	10	..	Pain, tumor	Expansion of shaft by non-radiating new bone, area of central destruction	Exploration, curetted	Proliferating chondroblasts	Dead 5 mos. later, autopsy
39750	W	M	15	11	Trauma, pain, tumor	Central rarefied area	Curetted	Calcification, giant cells	Living 24 mos.
39484	W	F	15	6	Pain, tumor	Central rarefied area	Curetted	Calcification, giant cells	Living 12 mos.
38452	W	F	20	12	Pain, tumor	Central rarefied area, soft part shadow	Curetted, toxins	Calcification, giant cells	Dead 9 mos. later
37882	W	F	14	2	Pain, limp	Subcortical rarefied area, soft part shadow	Amputation	Calcification, giant cells	Dead 21 mos. later
37670	W	M	20	..	Tumor	Subcortical rarefied area, soft part shadow	Amputation	Calcification	Dead 21 mos. later
36288	W	M	18	2	Pain, stiffness	Central rarefied area	Irradiation, amputation	Proliferating chondroblasts	Dead 21 mos. later
35226	W	M	16	1	Trauma, pain, tumor	Central rarefied area, periosteal roughening	Curetted twice, amputation	Calcification, giant cells	Dead 5 mos. later
33007	W	M	18	..	Tumor	Excision, radium, amputation	Calcification, giant cells	Dead 6 mos. later
32348	W	F	16	3	Trauma, pain	Rarefied areas, periosteal roughening, soft part shadow	Irradiation	Proliferating chondroblasts	Dead 6 mos. later
30168	W	F	18	2	Trauma, pain, tumor	Subcortical rarefied area	Amputation	Proliferating chondroblasts	Dead 1 mo. later, autopsy
28770	W	F	30	2	Pain	Rarefied area with periosteal reaction	Curettement, roentgen treatment, amputation	Calcification	Dead 13 mos. later
28661	W	M	16	5	Pain, limp, tumor	Subcortical rarefied area, periosteal roughening	Curetted, amputation	Proliferating chondroblasts	Well 8 yrs.
28399	W	M	11	12	Pain, swelling	Rarefied area with periosteal reaction	Curettement	Calcification, giant cells	Dead 7 mos. later
27509	W	F	20	2	Pain, tumor	Subcortical rarefied area, soft part shadow	Amputation	Proliferating chondroblasts	Well 4 yrs. lost from observation
26792	W	M	16	16	Trauma, pain	Central area of osseous destruction, periosteal roughening	Curetted, radium, toxins, irradiation	Calcification, giant cells	Dead 8 mos. later
23773	W	F	9	5	Pain, tumor, pathologic fractures	Central area of osseous destruction, periosteal roughening	Amputation	Proliferating chondroblasts	Well 8 yrs.
19897	W	F	16	2	Trauma, pain, tumor	Central osseous destruction, soft part shadow (from gross specimen)	Amputation	Calcified cartilage, giant cells	Dead 4 yrs. later
								Calcified cartilage, giant cells	Dead 3 mos. later

Roentgenologic Features.—The striking roentgenologic features of chondroblastic sarcoma are its relationship to an ossifying epiphyseal line and the association of a definite translucent periosteal reaction with a central area of multilocular osseous destruction. Not infrequently the tumor bears a marked similarity to the benign giant cell tumor in the x-ray film (fig. 35). Both lesions may cause central osseous destruction and involve an epiphysis of the long bone, but there are definite

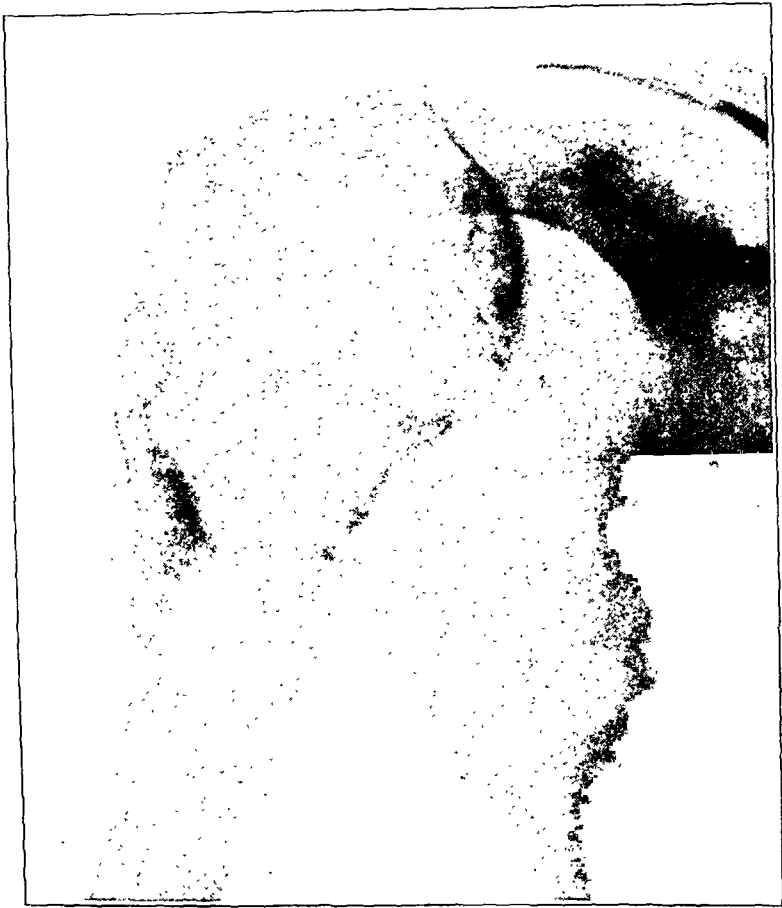


Fig. 35 (P. N. 26792).—Roentgenogram of a chondroblastic sarcoma extending on both sides of the epiphyseal line. The lesion shows the typical multilocular structure of a chondromatous growth, and, in addition, the periosteal reaction indicates its malignant character. This patient was cured by radium treatments following a curettement and the administration of Coley's toxins.

points of distinction. Whereas the giant cell tumor usually occurs in persons over 20, is confined largely to the epiphysis, is coarsely trabeculated in structure and produces little or no periosteal reaction even when perforating its bone shell, chondroblastic sarcoma usually occurs in patients under 20, extends on both sides of the epiphyseal line definitely invading the shaft, is finely multilocular in structure and is nearly always accompanied by a definite periosteal reaction (fig. 36). When

the earliest stages of this growth are studied by means of the roentgenogram, the involvement of the tumor is usually found to be primary in the metaphysis. From here it extends to involve the epiphysis in most cases, but may rarely invade the bone in the opposite direction toward the midshaft region (figs. 37 and 38). This peculiarity in the inception of the tumor indicates how intimately its origin is connected with the growth zones of the long bones, which, as is well known, are on the metaphyseal sides of the epiphyseal lines.



Fig. 36 (P. N. 35088).—Roentgenogram of a fatal chondroblastic sarcoma occurring in a white man, aged 24. This is an advanced stage of the lesion with a marked periosteal reaction and beginning pathologic fracture. The growth still shows a multilocular structure at its periphery in the epiphysis of the humerus.

While the tumorous area is predominantly central in location, there may occasionally be an escape beyond the cortex into the subperiosteal region, particularly near the epiphyseal line. In such instances the periosteum is raised by a translucent shadow, and osseous formation from the inner side of the periosteum is noticeably lacking.

The age distribution of this tumor aids in distinguishing it from a solitary focus of metastatic carcinoma. In cancer deposits that are

secondary in the bone, the localization of the involved area is usually nearer to the midshaft region, and the type of periosteal reaction seen in chondroblastic sarcoma together with the small subcortical zones of multiloculation is practically always absent. Also the involvement of the lower end of the femur, upper end of the tibia and lower end of the radius is rare in metastatic carcinoma while quite frequent in this form of chondrosarcoma.



Fig. 37 (P. N. 35226).—Roentgenogram of a chondroblastic sarcoma arising at the epiphyseal line and extending for some distance into the metaphysis. Note the small focus of osseous destruction in the epiphysis and the elongated area of rarefaction extending toward the shaft. This lesion proved rapidly fatal, and the patient died six months after the onset of the symptoms, in spite of amputation.

A Ewing's tumor may occasionally be a source of confusion. There is a similarity in the age of the patient, the acuteness of the symptoms and the tendency of the long bones to be the site of predilection. However, in Ewing's sarcoma there is more formation of new bone, a more diffuse involvement of the shaft with an extension to the midshaft

region, and the involvement of the epiphysis so characteristic of chondroblastic sarcoma is never seen in early cases.

Gross Pathology.—At operation, the tumor may be found extending into the soft parts covered by a thin envelope of fibrous tissue, invading the subperiosteal regions covered by an intact periosteum or entirely within a bone shell. In any event, the bulk of the neoplasm is usually within the medullary cavity or within a cancellous portion of the bone. The tumor tissue itself varies in consistency according to the degree of vascularity and necrosis. Often it gives an appearance of organized hemorrhage, being dark red or jelly-like in appearance,



Fig. 38 (P. N. 27509).—A chondroblastic sarcoma suggesting in the roentgenogram a Ewing's tumor. The lesion extends shaftward away from the epiphyseal line but definitely involves the epiphysis. There is a periosteal reaction resembling onion peel formation and slight sclerosis with widening of the shaft suggesting a Ewing's sarcoma. The small focus of the epiphyseal involvement is rare in Ewing's sarcoma. This case proved fatal within a year despite a disarticulation at the hip joint. For the microscopic picture see figure 43. *A* and *B* were taken before curettement. *C* was taken one week later.

and contains scattered bits of necrotic bone. At other times it is more consistent with gray or bluish-white, translucent areas resembling hyaline cartilage.

The mode of extension of the tumor is interesting. In some specimens in which the limb has been amputated, the unossified epiphyseal line can be clearly traced except at the point where there is proliferation

of the tumor (fig. 39). Here it is displaced by a hemorrhagic and necrotic mass which extends in irregular fashion into the metaphyseal region of the cancellous bone, stimulating little new osseous reaction. The tumor evidently does not disseminate as readily within the cancel-

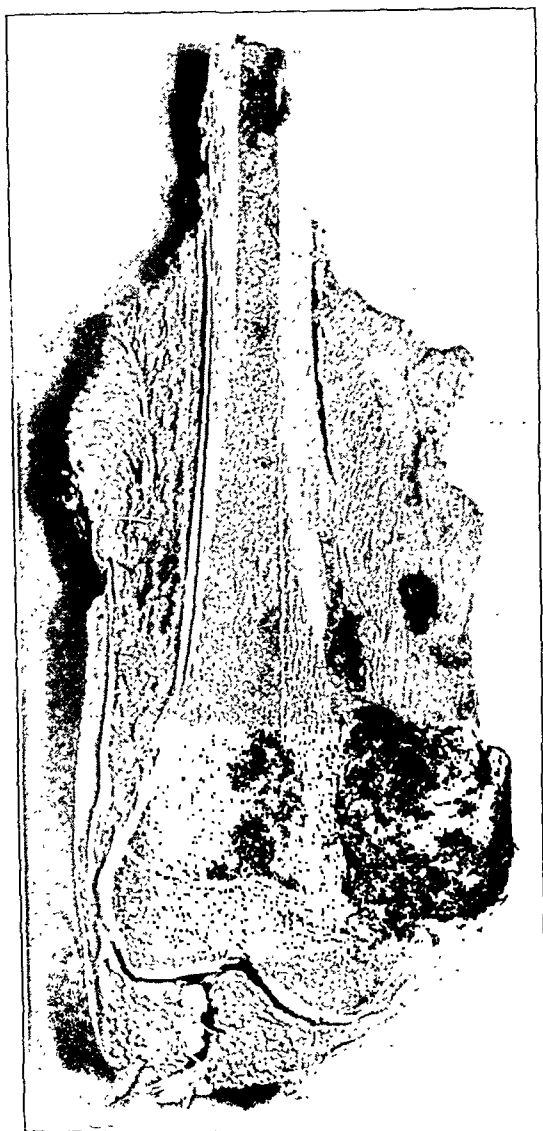


Fig. 39 (P. N. 35226).—A longitudinal section of the amputated specimen of the chondroblastic sarcoma shown in figure 37. The tumor had fungated through the operative wound made by two curettments. The relationship of the tumor mass to the unossified epiphyseal line is clearly discernible. Note the dark hemorrhagic character of the tissue.

lous bone as it does in the subperiosteal spaces, for once it has reached these areas the spotty medullary foci of tumor growth are replaced by a proliferating subperiosteal mass.

The most important information disclosed by the examination of the gross specimens is the continuity between the tumorous mass and the unossified epiphyseal line. The epiphyseal cartilage forms a plane of origin for the new growth, for whether the foci of invasion of the tumor extend into the metaphysis or into the epiphysis or laterally into the subperiosteal zone, a connection is always demonstrable between the area in which the epiphyseal cartilage is destroyed and the masses of tumor substance, provided the growth is not too far advanced.

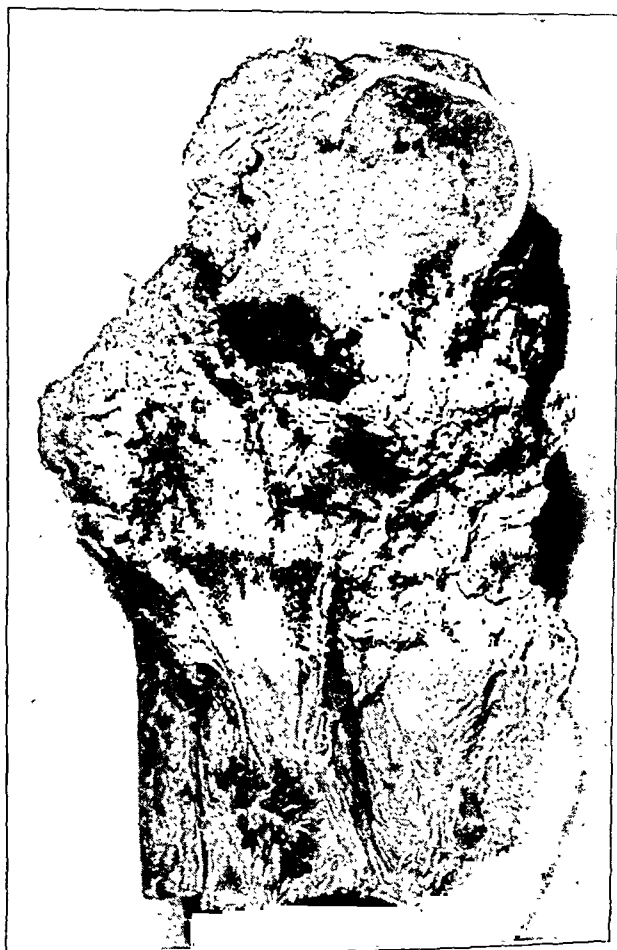


Fig. 40 (P. N. 23473).—A longitudinal section through the amputated specimen of a chondroblastic sarcoma involving the upper end of the humerus of a white girl, aged 9. The mass of tumor tissue has obliterated the metaphyseal region of the upper end of the humerus and partially invaded the epiphysis. A pathologic fracture has occurred through the vascular area. The upper part of the tumor is of cartilaginous consistency. This patient died four months after the amputation.

Clinically, the character of the tumor tissue found on exploration of these growths is often indistinguishable from the hemorrhagic grumous material found in giant cell tumor or the vascular cavitation in the so-called malignant aneurysms of the bone (fig. 40). But the

encountering of occasional zones of cartilaginous material in an otherwise necrotic and hemorrhagic mass or the connection of the tumor tissue with a persisting unossified epiphyseal line should always arouse suspicion of this rare form of chondroblastic sarcoma. Unlike the primary or secondary chondrosarcoma, syrupy, jelly-like masses of translucent chondromyxomatous material and cystic degeneration are not characteristic of this neoplasm.

Microscopic Features.—Under the microscope, chondroblastic sarcoma is essentially composed of a mass of young and adult cartilage cells undergoing calcification. The tissue, although distinctly of the hyaline cartilage variety as is indicated by the intercellular substance or matrix, differs from all forms of normal cartilage in its extreme vascularity (fig. 41). Strands of precartilaginous connective tissue with myxomatous formation and early fetal cartilage cells are absent, a point, which along with the vascularity, distinguishes this tumor under the microscope from the primary and secondary forms of chondromyxosarcoma just discussed. New bone of tumorous origin which may be sparsely present in chondromyxosarcoma is absent in these growths. The end-product of the tumor never passes beyond the stage of calcification—another important distinguishing microscopic feature. This last point is verified by a study of the metastatic pulmonary nodules, since normal reactive new bone may be present at the periosteal margins of chondroblastic sarcoma (figs. 42 and 43).

On examination with a high powered microscope, this sarcoma of the bone, which may be designated as calcifying chondrosarcoma as opposed to the chondromyxosarcomatous form which ossifies, presents an assortment of polyhedral and angular cells with prominent nuclei and ill defined cytoplasm. The younger cells show small dark nuclei with a crowded chromatin substance, while in the older cells the nuclei are larger and more vesicular with a distinct central nucleolus and a definite nuclear wall. Many of the cells have a scanty or ill defined cytoplasm, but in others there is a prolongation of cytoplasmic processes and within the meshwork of this reticulation a clear, faintly staining intercellular substance is often observed (fig. 44). This represents an attempt at the formation of typical cartilaginous areolae prior to the stage of calcification.

A characteristic and distinguishing histologic feature of these neoplasms is the intercellular lattice work formed by the calcifying matrix. This lattice work pervades the tumor with sketchy fragmentary curved lines, emphasized by varying degrees of calcium deposition. Here and there larger areas of uncalcified matrix appear which are easily recognized as typical hyaline cartilage, and in isolated portions of the tumor

circumscribed islands of chondroblasts may give the tumor an alveolar appearance. The tumor is extremely vascular with many blood spaces sparsely enclosed by a single layer of endothelium. Near these vascularized areas, and usually toward the periosteal margin of the growth, giant cell osteoclasts are numerous. These giant cells are of the epulis

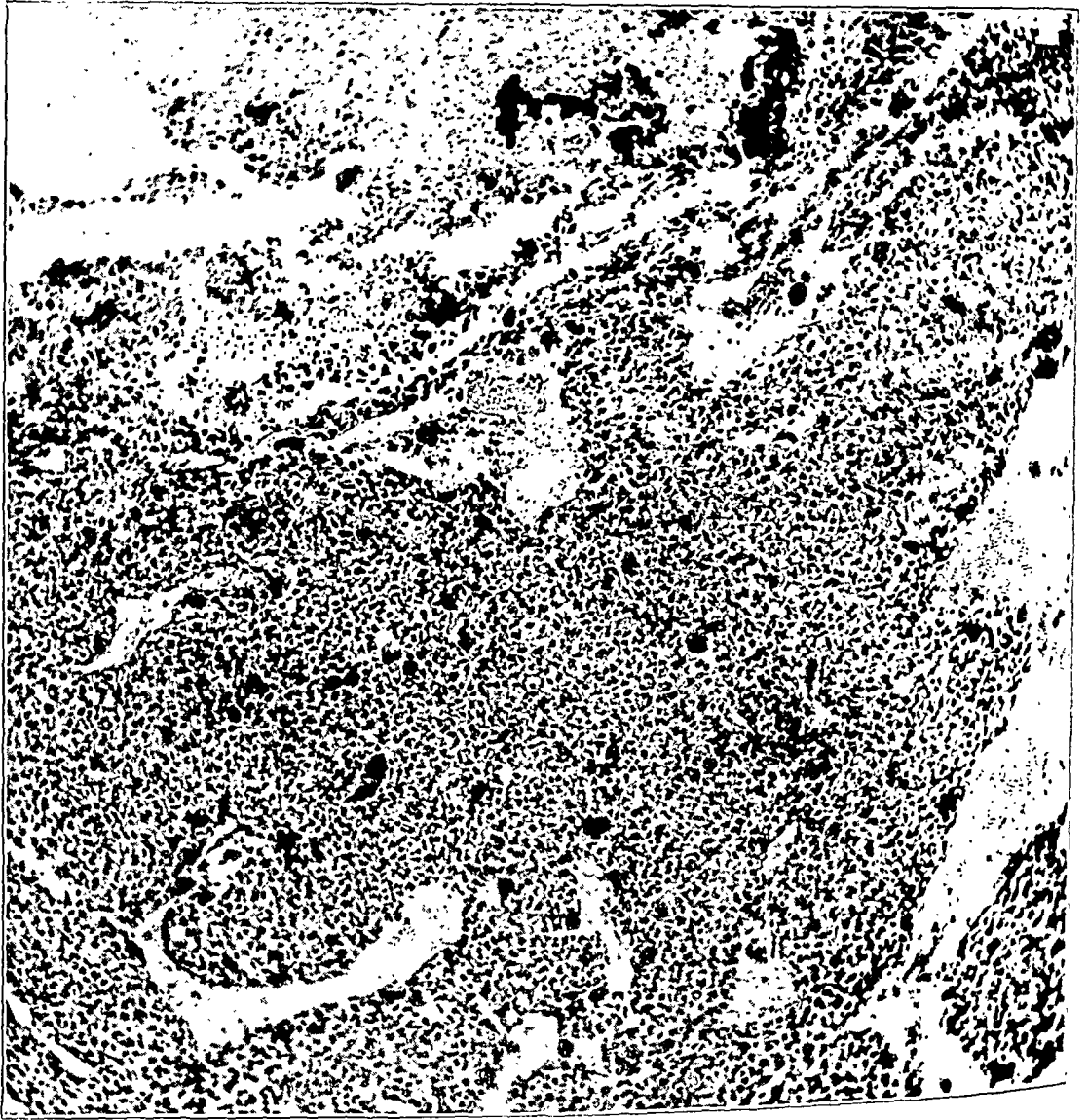


Fig. 41 (P. N. 35226).—Photomicrograph of a section taken from the tumor shown in figures 37 and 39. The section shows the proliferation of chondroblasts with a small amount of calcified cartilage. Vascularization and giant cell proliferation were marked in this case and originally led to an erroneous diagnosis of giant cell tumor.

type, and sections cut from the margins of these growths may closely simulate a benign giant cell tumor and have led in several instances to an erroneous microscopic diagnosis.



Fig. 42 (P. N. 32348).—Calcifying metastatic pulmonary nodule in chondroblastic sarcoma. The photomicrograph shows the end-stage of the tumorous process. Calcification but not new bone is produced. The patient was a white girl, aged 16, who died four months after the onset of symptoms.

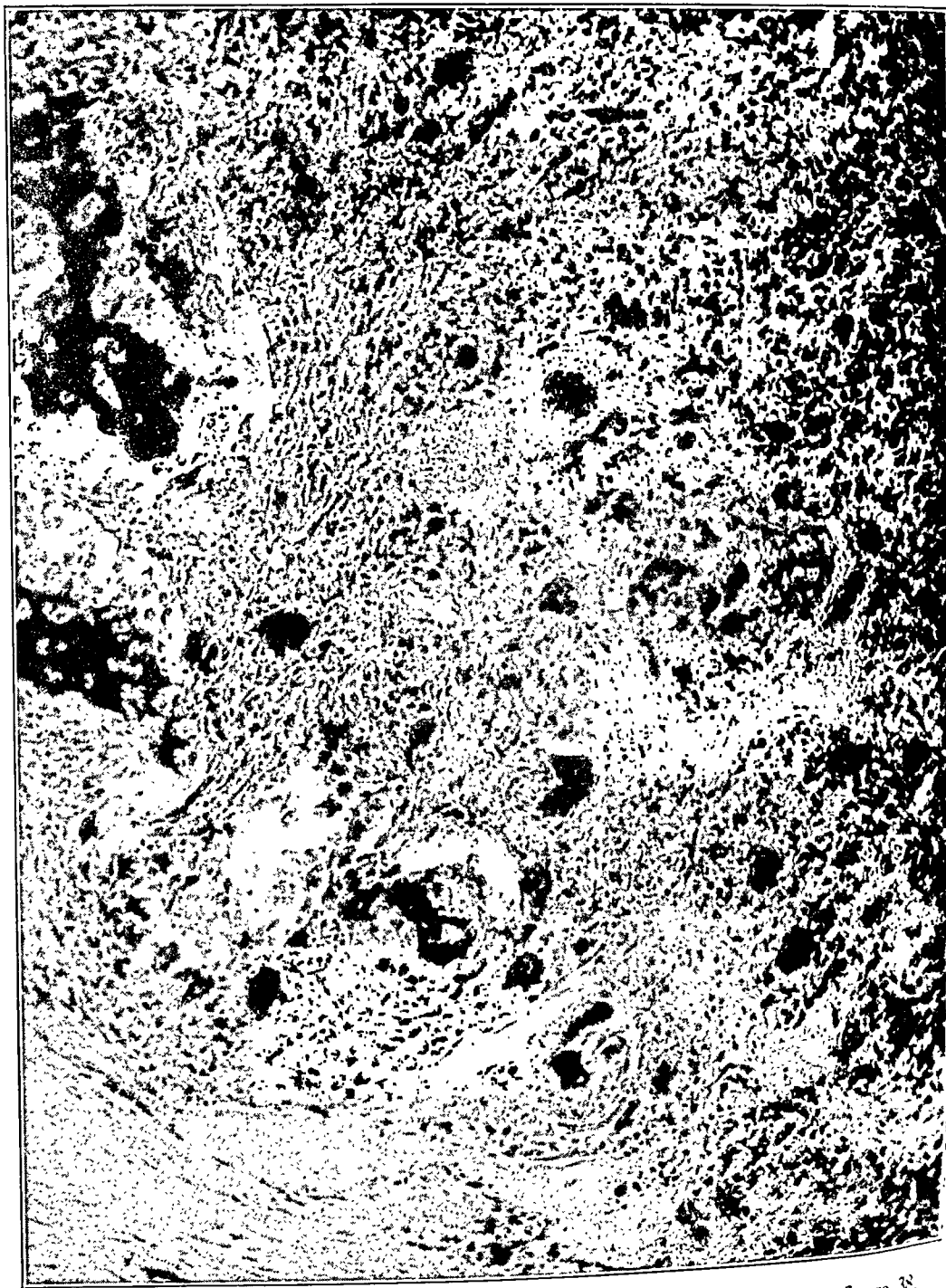


Fig. 43 (P. N. 27509).—Photomicrograph of the tumor shown in figure 38. Giant cell invasion of an area of the tumor undergoing calcification is taking place. The section was taken from the margin of the tumor.

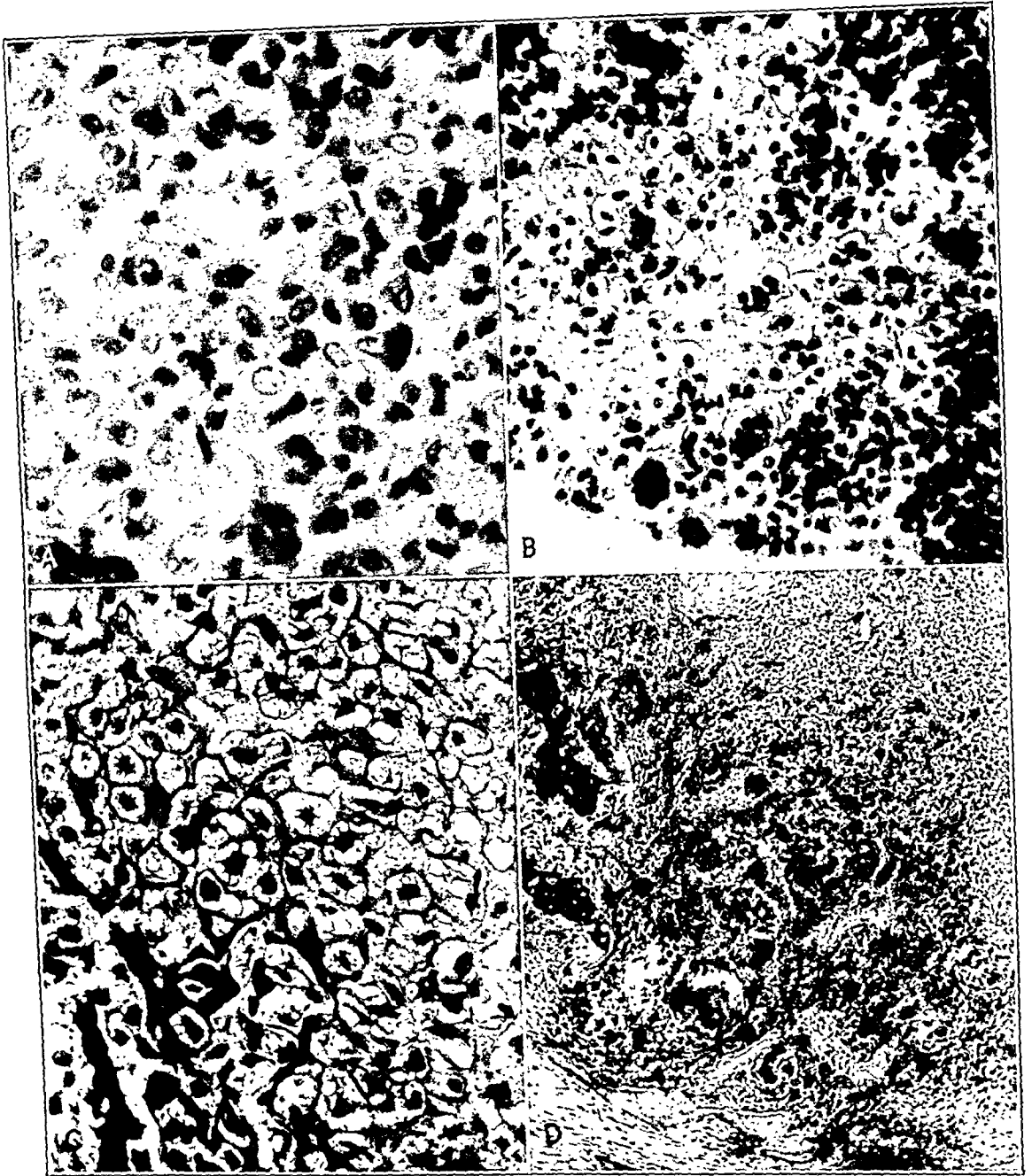


Fig. 44.—Microscopic studies of the histogenetic cycle of chondroblastic sarcoma. *A* shows the proliferation of chondroblasts with clear acidophilic cytoplasm surrounding nuclei of various sizes and represents the earliest stage. In *B*, a small amount of the matrix composed of hyaline cartilage is being formed. At *C*, the cartilage is undergoing rapid calcification. At *D*, the periosteal margin of the tumor is shown. The periosteum is reacting with a slight amount of new bone formation, and the tumor is being invaded by giant cells, which in all probability represent a defensive reaction against the calcifying tumor mass.



Fig. 45.—Comparison of the neoplastic chondral tissue in chondroblastic sarcoma with the cartilaginous skeleton of the embryo. *A* shows chondroblastic proliferation in the human embryo, and *B*, early calcifying cartilage in the same embryo. *C* shows chondroblastic proliferation in a chondroblastic sarcoma, and *D*, early calcifying cartilage in the same tumor. These photographs indicate quite emphatically that the neoplastic process concerns the proliferation of chondral elements, and that the giant cell areas often seen in the sections are a secondary phenomenon.

HISTOGENESIS

The age incidence of this tumor, its location at an active epiphyseal line and the easy identification of the proliferating cartilage cells as chondroblasts similar in type to those present in the skeleton of the embryo immediately after the long bones have been preformed in cartilage, supply the clues necessary to an analysis of the histogenesis (fig. 45).

In the adolescent age period in normal persons, there is at the epiphyseal lines of the upper end of the humerus, lower end of the femur, upper end of the tibia and lower end of the radius where these tumors predominate a final spurt of growth in the length of the appendicular skeleton previous to the obliteration of the growth disks. This spurt in development in the long bones takes place on the metaphyseal side of the epiphyseal line and is accomplished by a twofold process. There is a reproduction of cartilage cells in the form of chondroblastic proliferation, and in addition to this reproduction there is a maturation and further development of the cartilage cells terminating in calcification. Later vascularization with resorption of the calcified material takes place to be followed by the substitution of permanent new bone. In this final process of substitution, brought about by new blood vessels and the resorptive power of giant cell osteoclasts, the cartilage cells play no active rôle, but constitute in their calcified state a necessary stimulus to the final event of ossification. This entire process, which normally is gradual and orderly, is distorted and tremendously hurried and exaggerated by the etiologic factors that precipitate the malignant growth.

The malignant growth coincides, therefore, at its inception with the normal developmental process at the epiphyseal line, but departs from the normal in that a single line of cell differentiation predominates, creating a definite unbalance in favor of chondroblastic growth and calcification.

The result of this malignant distortion is a tumor characterized by rapidly proliferating chondroblasts that abort into an end-stage of calcified cartilage without producing, except in a fragmentary way, the usual hyaline matrix typical of adult cartilage in the normal development. Apparently while still in a proliferating stage, many chondroblasts of the malignant type are ensnared in a calcifying matrix of their own making and are petrified.

The vascularity of the tumor and the giant cell areas are secondary features. Giant cell invasion followed by vascular channels is the normal order of embryology in the osteogenesis of permanent bone via the intermediate route of cartilage (Geschickter and Copeland²⁵).

25. Geschickter, C. F., and Copeland, M. M.: Osteitis Fibrosa and Giant Cell Tumor. *Arch. Surg.* 19:169 (Aug.) 1929.

Apparently, in this tumor the invasion of the calcified structures by giant cells and blood capillaries is a normal defensive response on the part of the adjacent periosteum as is evidenced by the fact that such areas are always more pronounced at the margin of the tumor and are notably lacking in metastatic pulmonary nodules where an end-stage of unresorbed deposits of calcium is the rule (figs. 42 and 43). A portion of the vascularity (mainly vessels of the thin endothelial wall type), however, must be looked on as a feature common to sarcoma in general.²⁶ The presence of these vascular areas of giant cells accounts for the frequent mistakes by competent pathologists in diagnosing these neoplasms as benign giant cell tumor, metastatic giant cell tumor and angiosarcoma. The classification by Codman²⁰ of these tumors as benign epiphyseal chondromatous giant cell tumors peculiar to the upper end of the humerus is not supported by the present study. In the first place we find a wider distribution for these lesions and proved instances of death produced by pulmonary metastases, in spite of radical operation. Secondly, the cartilage present cannot be considered as a passive structure, representing a persistence of the normal unossified epiphyseal line. The chondral elements are actively proliferating, and the chondroblasts have definite invasive powers. These chondroblasts and the transitional forms they show are not characteristic of the normal epiphysis, but resemble the cells seen in the embryo when the skeleton is being preformed in rapidly growing cartilage.

PROGNOSIS AND TREATMENT

The duration of symptoms and the clinical follow-up emphasize the malignant character of this calcifying form of chondrosarcoma. The usual duration of the disease from the onset of the first symptoms to death does not exceed two years. With present standards of diagnosis and methods of treatment, the outlook is not favorable. Of fourteen cases in this series in which amputation was performed all but one terminated fatally. One patient survived the operation more than twenty-one months, only to succumb to metastasis.

Considering the malignancy of the growth, an unusual number of the patients were treated by curettement with or without cauterization, in most instances owing to faulty diagnosis. None of these patients was

26. This view, that the giant cell areas in chondroblastic sarcoma are a product of normal reacting bone, it is believed, is nearer the truth than the supposition that they are a further stage in the malignant osteogenesis of cartilaginous bone by the sarcomatous chondroblasts. Since the death of the chondroblasts with the formation of the calcified matrix can be observed under the microscope, it is difficult to see how they could survive to initiate the giant cell phase, as a further malignant product. The fact that giant cells are more numerous at the margin of the tumor at the site of normal reactive bone supports this view.

benefited by this mode of therapy when used alone. Two patients, curetted and treated by erysipelas and prodigiosus toxins (Coley's), died three and nine months, respectively, after the procedure was instituted.

Although preoperative or postoperative irradiation failed in the majority of cases wherein it was used, the only two five year cures recorded in this series were in patients subjected to this mode of therapy in addition to surgical measures. In one, radium as well as deep roentgen therapy was employed, the radium being implanted directly into the operative wound after curettage. This patient also received Coley's toxins. In the other case, a thorough course of deep roentgen therapy followed the curettement, and in addition, amputation was finally performed. While both deep roentgen therapy and radium have failed (one patient treated by direct radium implants died of tumor nineteen months after treatment was begun), irradiation should not be neglected as a counterpart to operation in these cases of chondroblastic sarcoma.²⁷ This is borne out by a follow-up study in nearly 200 cases of the various chondrosarcoma groups (primary, secondary and chondroblastic). The conclusion seems warranted that unless an early amputation can be performed, operative intervention should always be followed by irradiation, preferably by competent radium therapy. The radium dosage, however, must be adequate and should not be attempted unless at least 120 mg. are available.

CONCLUSIONS CONCERNING THE CHONDRAL FORMS OF OSTEOGENIC SARCOMA

In the chondral forms of osteogenic sarcoma that have been discussed, there is little choice between the various types from the standpoint of prognosis so far as *microscopic* examination is concerned. Whether the microscope discloses a combination of primitive connective tissue, myxoma, fetal, adult cartilage and new bone characteristic of primary myxochondrosarcoma, or whether it reveals a tumor composed of proliferating chondroblasts with abortive and calcifying cartilage typical of chondroblastic sarcoma, the outlook is equally grave. There is, to be sure, slightly more chance of permanent cure in the chondroblastic form which would be expected on the basis of microscopic grad-

27. Two additional cases in which cure was obtained have been added to this group of tumors by Codman in his study of the material from the Bone Registry. Two other cases are reported by him in which the patients were alive, two years and four months and three years and ten months, respectively. In the cases in which cure was obtained, resection following two recurrences was effective in one, and in the other the patient is reported well following exploration and treatment by erysipelas and prodigiosus toxins (Coley's). From his studies, Codman doubts the malignancy of this group, but the cases reviewed by him included only those occurring in the upper end of the humerus.

ing, since in chondroblastic sarcoma the mother cell represents a higher stage of differentiation than does the precartilaginous connective tissue giving rise to chondromyxosarcoma.

However, far more significant than the microscopic structure from the standpoint of the grading of the degrees of malignancy in these sarcomas is the *clinical* question of whether the tumor is of primary or secondary origin. As can be seen from table 3, the five year cures are from two to three times as great among the chondrosarcomas of secondary origin as in either the primary or chondroblastic forms. In view of the fact that it is usually impossible to distinguish under the microscope between the primary and secondary forms of chondromyxosarcoma, the question arises: To what is this difference in the degree of malignancy to be ascribed?

TABLE 3.—*Comparison of Results of Treatment in the Chondral Forms of Osteogenic Sarcoma*

Results in 186 Chondral Sarcomas	Primary Chondrosarcoma	Secondary Chondrosarcoma	Chondroblastic Sarcoma
Total.....	84	80	24
Lost.....	4	7	1
Total followed.....	80	73	23
Followed over 5 years.....	40	50	18
Well over 5 years.....	2	12	2
Per cent of 5 year cures.....	5%	24%	11%

Since all of these chondral sarcomas (as well as the osteogenic sarcomas as a group) arise in tissue capable of further differentiation, and since the tumorous process itself apparently involves this differentiation, whether this process is at the height of its activity due to an impetus to normal growth or whether it is in a relatively quiescent state, constituting, as it were, a cell rest in the sense of Cohnheim, is of fundamental importance to the subsequent course of the growth. In the very malignant tumors of primary chondrosarcoma and chondroblastic sarcoma, the tissue of origin represents a zone of active growth. In the primary chondromyxosarcomas, the precartilaginous connective tissue forms a junction between osseous tissue and the ends of tendons that attach directly to bone and act as a zone of growth interposed between the two maintaining connection with the lengthening tendon as the bone grows. There is, therefore, an impetus to normal growth behind the primary chondromyxosarcomas that arise at these sites during youth and the adolescent period. In the same way there is a corresponding impetus behind the chondroblastic sarcomas that arise at a similar zone of normal growth at the epiphyseal line during the same age period.

On the other hand, in the secondary chondromyxosarcomas, which are common in patients beyond the age of 30, the undifferentiated tissue.

which acts as a source for the malignancy, bears no relation to either an age period of active growth or to a zone of normal growth. Instead, a benign osteochondroma or chondroma (which is usually a congenital defect) harbors the undifferentiated tissue in a quiescent state, and not until some local injury stimulating a reparative process occurs does the sarcomatous growth arise.

From an analysis of the chondral forms of sarcomas, therefore, it may be concluded that the osteogenic sarcomas of the bone, as a group, are intimately connected with the process of histogenesis. These sarcomas arise either during a process of differentiation in tissue at a zone of growth during the normal period for growth or in an embryonic rest from relatively undifferentiated tissue persisting in a quiescent state in some benign tumor of the bone. In the following discussion of the forms of osteogenic sarcoma of fibro-osseous origin, these conclusions will be seen to apply to both the early type of osteolytic sarcoma and the later form of sclerosing periosteal sarcoma.

From the standpoint of the degree of malignancy in the grading of all these tumors, the same principles apply. The degree of malignancy depends not only on the degree of differentiation of the cell of origin, but on whether or not the process of differentiation is concerned with an impetus to normal growth. To state this differently, the grading of the neoplasm is a function of the age of the cell from the embryonic standpoint and a function of the age of the patient from the standpoint of general bodily growth.

(To be Concluded)

THE SEDIMENTATION TEST OF THE BLOOD IN GENERAL SURGERY

WITH SPECIAL REFERENCE TO DISEASE IN THE LOWER RIGHT
QUADRANT AND TO THE MECHANISMS INVOLVED *

MANUEL GRODINSKY, M.D.

ОМАНА

If whole blood to which some anticoagulant, such as sodium citrate, has been added is allowed to stand in a test tube, the erythrocytes (and leukocytes) will gradually settle, leaving a clear plasma above. That there is a marked variation in the settling time of blood in health and in inflammatory conditions has been noted by many observers. Galen spoke of the erythrocytes as forming a buffy coat or "crusta phlogista." In 1791, John Hunter noted that the erythrocytes of blood settled more quickly in inflammatory conditions than in normal blood, and that the red cells of normal blood, separated from their own plasma and transferred to the plasma of infected blood, settled with greater speed, the rate being in direct relation to the severity of the infection. This observation became the stimulus for numerous investigations and reports both in this country and abroad (Müller, 1844; Davy, 1839; Nasse, 1836, and others). Then, as often happens in medicine, interest in this phenomenon lagged for half a century, only to be awakened again in 1917, when Fahræus accidentally noticed the rapidity of the sedimentation of red corpuscles in the citrated blood of gravid women. Later, he as well as Linzenmeier (1920-1922) found the rapidity of sedimentation even more increased in patients with infections, Linzenmeier giving particular attention to pyosalpinx.

Friedlaender (1924), Polak (1926) and Baer and Reis (1926) have given an excellent review of the literature and have demonstrated the great value of the test in obstetric and gynecologic cases. Wehrbein (1928) has shown its value in urology. It is my purpose to attempt to evaluate the test in general surgery, with special reference to disease in the lower right quadrant of the abdomen and to the mechanisms involved. During the past two and one-half years, sedimentation tests have been made on most of the patients admitted to the surgical wards of the University Hospital. Complete blood counts including Schilling counts were made at the same time for comparison. When Schilling

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determinations were not made, ordinary differential counts and counts of polymorphonuclear leukocytes, as shown in the segmented cell column of the tables, were substituted.

METHOD

The technic employed in this study was that of Linzenmeier (1922), as modified by Friedlaender (1924). Eight-tenths cubic centimeter of blood was drawn directly from a vein with a Luer syringe containing 0.2 cc. of a freshly prepared 5 per cent solution of sodium citrate. The blood and citrate solution was shaken in the syringe until thoroughly mixed and then emptied into a sedimentation tube. This tube is simply a hard glass tube about 6.5 cm. in length and 5 mm. in diameter which has been marked at the 1 cc. level and at 6, 12, 18 and 24 mm. below this level. The time was noted when the mixture was placed in the tube and likewise when the line of demarcation between the erythrocytes and plasma reached the 6, 12, 18 and 24 mm. marks, respectively. In order to have a direct comparison with most previously reported results, the time required for the demarcation line to reach the 18 mm. mark was used in this report, although additional information may be gained by plotting a curve of the entire settling time (Cutler, 1926; Kilduffe, 1929). Such a curve usually shows a relatively slow settling from 0 to 6 mm. (probably due to surface tension), a more rapid fall from 6 to 12 and from 12 to 18 mm., and again a slower time from 18 to 24 mm. (probably due to packing of cells).

Normal Sedimentation Time.—Before a test may be of value in disease, a normal for that test must be established. In more than 300 cases of healthy persons, Friedlaender found the sedimentation time (18 mm. line) to be from 1,000 to 1,200 minutes in the male and from 600 to 1,000 minutes in the female. The values given by Linzenmeier are somewhat higher. On the other hand, others report lower figures, some regarding readings over 200 minutes as normal. In healthy persons our average is 720 minutes, varying between 300 and 1,450 minutes. It must be remembered that in an apparently healthy person some form of infection may be hiding which may accelerate the sedimentation time. In spite of this apparent discrepancy in supposedly normal persons, there is such a marked acceleration in certain conditions of disease that it is not as difficult to draw the line between normal and abnormal as it may seem at first. For purposes of this study, any time under 200 minutes may be considered as having diagnostic and prognostic significance.

SEDIMENTATION RATES IN VARIOUS CONDITIONS

Inflammatory Pelvic Diseases.—Table 1 shows the sedimentation time, total leukocyte count and differential (Schilling) count in a representative group of acute, subacute and chronic inflammatory pelvic conditions. Practically all cases of acute salpingitis, tubo-ovarian abscesses and cul-de-sac abscesses showed a sedimentation time of less than 30 minutes. In the subacute cases of the same nature, the sedimentation rates were approximately between 30 and 60 minutes, and in the chronic cases, between 60 and 120 minutes. The leukocyte count and the differential count for the most part were consistent with the sedimentation time. However, there were some glaring discrepancies. For instance, in a subacute case of salpingitis (proved by operation), there were a

sedimentation time of 34 minutes and a total leukocyte count of 7,300; in a case of septic abortion, a sedimentation time of 15 minutes and a leukocyte count of 8,300, and in a chronic case of salpingitis (operative),

TABLE 1.—*Inflammatory Pelvic Diseases*

Case	Sedimentation Time	White Blood Cells	Segmented Cells	Staff Cells	Young Cells	Lymphocytes	Mono-cytes	Eosino-phils	Baso-phils	Diagnosis
M. M.	20	17,950	71	23	..	5	1	Acute and subacute salpingitis
	17	12,600	58	15	5	17	3	2	..	
M. S.	37	6,600	60	30	3	7	..	
O. B.	20 1/4	12,500	53	15	3	24	3	2	..	
A. P.	12	26,400	92	8	Pelvic abscess
R. G.	20	17,400	37	49	4	5	5	Acute salpingitis
E. W.	13	13,600	38	32	..	23	3	4	..	Acute salpingitis
	35	32,600	78	12	..	6	4	Acute salpingitis
	25	20,200	57	16	8	16	1	1	1	Acute and subacute salpingitis
	17	19,100	77	23	
	42	16,000	44	7	2	35	8	3	..	
M. B.	72	13,800	56	15	..	27	1	1	1	
M. S.	20	26,400	92	8	
	15	22,000	74	20	2	Acute salpingitis
M. K.	26	9,300	53	4	..	33	5	Acute salpingitis
L. K.	15	8,300	54	17	4	27	2	..	1	
M. T.	26	18,700	56	26	..	13	5	Septic abortion
M. S.	21	10,800	74	10	..	13	1	Tubo-ovarian abscess
S. T.	12	27,900	72	19	2	3	4	Acute salpingitis
M. F.	9	10,000	51	7	..	35	6	1	..	Tubo-ovarian abscess
M. O.	18	22,800	59	26	1	13	1	Acute salpingitis
M. W.	23	16,200	54	32	..	10	4	Pelvic abscess
M. H.	19	18,200	37	37	1	21	2	2	..	Acute salpingitis
M. S.	28	13,500	63	5	1	23	5	1	2	Pelvic peritonitis
M. W.	17	16,000	70	16	2	9	2	1	..	Acute salpingitis
M. B.	31	18,500	55	32	4	8	1	Bilateral pyosalpinx
M. R.	26	18,200	82	18	Septic abortion
M. W.	30	16,000	55	22	3	15	3	1	1	Acute salpingitis
M. W. H.	15	15,000	84	16	Pyosalpinx
M. K.	13	13,000	80	20	Pelvic abscess
V. R.	15	15,050	86	14	Acute salpingitis
M. J.	15	12,000	66	6	2	19	1	5	1	Acute salpingitis
M. B.	16	14,000	50	25	2	18	3	1	1	Acute salpingitis
M. M.	20	11,750	47	28	6	19	Septic abortion
M. S.	10	10,500	64	4	7	23	2	Tubo-ovarian abscess
M. Q.	25	15,200	82	17	1	Septic abortion
M. B.	14	16,500	25	35	29	10	..	1	..	Puerperal sepsis
M. E.	58	10,600	70	1	1	20	5	2	1	Subacute salpingitis
M. S.	36	7,600	60	5	..	32	3	Subacute salpingitis
M. H.	59	10,500	75	25	Subacute salpingitis
F. H.	33	7,600	78	16	6	Subacute salpingitis
B. C.	42	7,800	74	24	2	Subacute salpingitis
M. A.	30	10,400	65	35	Subacute salpingitis
M. S.	37	13,600	54	4	7	25	9	..	1	Subacute salpingitis
M. B.	28	10,300	63	10	..	23	4	Subacute salpingitis
M. I.	27	11,000	74	24	2	Subacute salpingitis
M. S.	35	8,750	56	12	5	18	6	2	1	Subacute salpingitis
M. B.	28	11,400	76	23	1	Incomplete abortion
M. B.	29	7,600	72	22	6	Subacute salpingitis
M. N.	27	11,000	69	2	..	25	3	1	..	Subacute salpingitis
B. B.	34	7,300	44	30	4	16	4	2	..	Subacute salpingitis
M. W.	42	9,000	59	19	1	16	2	2	1	Subacute salpingitis
M. S.	120	7,300	59	34	6	1	..	Chronic salpingitis
G. S.	114	10,250	61	36	2	1	..	Chronic salpingitis
V. P.	58	7,850	74	23	1	2	..	Chronic salpingitis
B. A.	106	10,100	52	15	..	30	3	Chronic salpingitis
M. C.	71	10,400	65	35	Chronic salpingitis
M. C.	92	11,600	63	2	1	29	5	Chronic salpingitis
M. C.	111	9,640	71	28	1	Chronic salpingitis
M. W.	126	13,200	69	13	2	13	3	Chronic salpingitis
A. W.	79	12,000	57	17	1	19	5	1	..	Chronic salpingitis

a sedimentation time of 126 minutes and a leukocyte count of 13,200. In some cases, the differential count (Schilling) fitted in with the sedimentation time better than the total white count (for example, a sedimentation rate of 34 minutes, a leukocyte count of 7,300 and Schilling determination: segmented cells, 44; staff cells, 30; young cells, 4;

lymphocytes, 16; monocytes, 4, and eosinophils, 2), but in others it was also at variance (for example, a sedimentation rate of 36 minutes, a leukocyte count of 7,600 and Schilling determinations: segmented cells, 60; staff cells, 5; young cells, 0; lymphocytes, 32, and monocytes, 3). With due consideration of possible errors in technic and judgment, particularly as regards the Schilling count, there is still a group of cases in which a marked discrepancy exists between the sedimentation time and the blood picture. From a diagnostic and prognostic standpoint, the sedimentation test is a valuable adjunct to the total white and differential blood counts, often exceeding them in importance. In the differential diagnosis between appendicitis and right-sided adnexal dis-

TABLE 2.—*Noninflammatory Pelvic Diseases*

Case	Sedimentation Time	White Blood Cells	Segmented Cells	Staff Cells	Young Cells	Lymphocytes	Monocytes	Eosinophils	Basophils	Diagnosis
M. C.	135	7,300	63	4	..	21	11	1	..	Retrodisplacement
M. C. A.	229	8,900	57	6	..	35	2	Retrocele, cystocele
M. F.	204	9,400	63	35	2	Simple fibroid tumor
M. W.	438	7,950	69	31	Cystic ovary and fibroid tumor
M. B.	73	7,800	78	22	Retrodisplacement
M. S.	240	10,200	61	36	2	1	..	Retrodisplacement
M. B.	50	7,500	58	39	3	Fibroid tumor
M. H.	61	6,450	65	31	1	2	1	Prolapsus uteri
P. C.	131	6,200	55	4	2	38	1	Prolapsus uteri
S. E.	83	9,850	66	32	2	Fibroid tumor (diabetes)
D. P.	181	15,600	74	22	3	1	..	Procidencia
M. C.	31	8,900	57	15	..	27	1	Fibroid with abscess
M. H.	14	19,700	68	18	1	13	Infected fibroid tumor
M. L.	45	11,800	72	8	2	15	3	Ectopic pregnancy, uncomplicated
H. B.	26	13,000	60	15	5	15	4	1	..	Ectopic pregnancy with adnexal disease

ease, it is of particular value, as will be shown later. Friedlaender, Polak and Baer and Reis used the test in determining the safe time for operation in inflammatory pelvic diseases. Baer and Reis arbitrarily took 60 minutes as the deadline under which operation was not safe. In our experience, the patients with a sedimentation time under 60 minutes who were operated on had a stormier convalescence than those who were not operated on until the settling rate was over 60 minutes. However, operations in cases with sedimentation rates as rapid as 30 minutes were safe, although there were a few days of severe reaction. In our series, cases in which the settling time was under 30 minutes were considered inoperable at this stage.

Noninflammatory Pelvic Conditions.—Patients with simple ovarian cysts, perineal lacerations, displacements and uncomplicated fibroids showed normal sedimentation time unless there were other foci of infection (table 2). On the other hand, in cases of infected fibroids or fibroids associated with adnexal disease the sedimentation time was rapid. In uncomplicated ectopic pregnancy, there was a moderately

accelerated sedimentation (45 minutes), but when associated with salpingitis a much more rapid time (26 minutes) was noted.

Diseases of the Urinary Tract.—In acute infections of the urinary tract, such as pyelitis, pyelonephritis, pyonephrosis, prostatitis and perinephritic abscess, rapid sedimentation times (under 30 minutes) were noted without exception (table 3). Usually the total leukocyte count and the Schilling count were in accord, but in two cases of pyonephrosis with urinary fistulas, the rapid sedimentation times were associated with fairly normal blood pictures. On the other hand, ureteral colic (stone) and other urologic conditions without associated gross infection were accompanied by fairly normal sedimentation times, emphasizing the importance of the latter in the differential diagnosis of pain in the lower right quadrant of the abdomen.

TABLE 3.—*Urinary Tract Disease*

Case	Sedimentation Time	White Blood Cells	Segmented Cells	Staff Cells	Young Cells	Lymphocytes	Mono-cytes	Eosinophils	Basophils	Diagnosis
M. A.	234	9,600	67	9	..	21	..	1	2	Renal calculus
E. N.	76	6,000	43	20	4	28	5	Essential hematuria
W. H.	16	14,200	46	24	18	7	4	1	..	Pyonephrosis
M. B.	9	10,300	86	14	Pyonephrosis
M. R.	18	7,100	40	36	4	20	Acute hemorrhagic nephritis
M. C.	13	16,000	85	14	1	Infected prostate
M. W.	17	6,300	47	13	4	31	4	1	..	Urinary fistula
D. L.	17	12,600	69	15	..	15	1	Perinephritic abscess
M. W.	16	7,100	42	28	1	23	6	Urinary fistula
L. M. M.	18	9,700	56	8	..	30	6	Infected hydrocele
L. C.	17	10,500	Pyelonephritis
M. W.	30	15,400	79	21	Pyonephrosis
B. M.	150	8,400	70	30	Ureteral calculus
A. K.	300	7,200	68	32	Ureteral calculus
M. P.	8	11,200	80	16	4	Pyonephrosis
J. G.	430	9,300	73	27	Ureteral calculus

Appendicitis.—Perhaps the most interesting and valuable finding is the relatively slow sedimentation time present in acute appendicitis without rupture. In a fairly representative series of cases (table 4) the average was 115 minutes, with variations between 45 and 300 minutes. In the subacute and chronic forms, there were even slower times, averaging 227 minutes, with variations between 51 and 540 minutes. As already noted, in right-sided inflammatory adnexal and urinary tract diseases there are more rapid sedimentation rates. Although the total white count and differential count are often valuable in differentiating these conditions from appendicitis, there is still a considerable group of cases in which such counts are either not characteristic or are borderline, making them misleading or valueless in the differential diagnosis. It is in this group particularly that the sedimentation test is often of the greatest value in helping to establish the true diagnosis. Of course, no diagnosis should be based on a single finding, but on a combined picture built up by a complete history, a thorough physical examination and indicated

TABLE 4.—*Appendicitis*

Case	Sedimen- tation Time	White Blood Cells	Seg- mented Cells	Staff Cells	Young Cells	Lym- pho- cytes	Mono- cytes	Eosino- phils	Baso- phils	Diagnosis
L. M. K.	61	7,200	54	13	1	26	5	1	..	Acute (pregnancy)
M. K.	103	11,600	47	20	4	23	6	Acute
M. C.	180	15,400	84	13	3	Acute
M. C.	200	14,100	82	18	Acute
M. D.	48	7,600	52	6	3	35	1	3	..	Acute
L. J.	256	19,600	58	26	3	10	2	..	1	Acute
M. L.	131	18,200	54	32	3	7	4	Acute
M. M.	51	14,000	66	17	5	6	6	Acute
H. H.	58	14,000	48	19	4	23	6	Acute
M. P.	77	18,600	49	7	..	42	2	Acute
M. S.	52	13,000	49	13	1	23	4	9	1	Acute
E. H.	300	22,800	96	4	Acute
W. P.	240	18,300	91	9	Acute
O. H.	50	26,700	57	23	5	5	10	Acute
V. H.	150	13,200	58	32	..	6	4	Acute
A. P.	45	17,400	37	49	4	5	5	Acute
F. H.	170	17,000	34	4	..	56	4	2	..	Acute
M. S.	45	17,500	56	29	..	12	2	1	..	Acute
C. K.	148	16,100	73	21	4	..	2	Acute
H. B.	46	15,600	59	11	5	20	4	1	..	Acute
E. S.	142	11,800	78	22	Acute
L. F.	35	12,400	55	20	1	16	8	Acute (throat infec- tion)
F. J.	150	10,200	63	16	..	14	5	2	..	Acute
M. M.	160	13,200	52	24	..	22	..	2	..	Acute
M. H.	75	10,000	76	24	Acute
E. C.	52	7,800	46	6	..	40	..	8	..	Acute
L. M. J.	100	14,800	33	26	..	34	4	3	..	Acute
M. T.	51	4,600	47	15	1	33	3	1	..	Subacute
M. W.	191	8,600	46	16	1	36	1	Subacute
D. D.	63	5,150	55	15	2	21	4	3	..	Subacute
M. H.	153	8,300	52	14	..	27	4	3	..	Subacute
M. J.	257	8,200	58	12	..	28	2	Subacute
M. N.	225	10,800	64	6	1	24	4	1	..	Subacute
A. H.	180	5,200	60	40	Subacute
V. H.	194	6,800	60	40	Subacute
D. R.	258	10,400	41	1	2	55	1	Subacute
L. S.	80	9,800	46	18	..	29	5	2	..	Subacute
N. C.	93	7,600	57	8	..	27	6	2	..	Subacute
M. M.	193	6,200	64	23	8	5	..	Subacute
C. S.	80	8,800	52	22	..	20	2	4	..	Subacute
J. R.	34	7,600	49	13	..	29	9	Subacute (active syphilis)
E. T.	180	9,600	42	2	1	33	13	8	1	Subacute
R. C.	185	9,250	58	10	4	20	5	2	1	Subacute
R. H.	360	7,400	42	4	..	50	4	Chronic
F. G.	26	8,200	62	30	5	2	1	Chronic (throat infection)
H. G.	240	9,000	70	25	5	Chronic
V. A.	210	4,600	46	6	..	37	8	3	..	Chronic
M. S.	28	9,600	61	12	..	21	5	1	..	Chronic (complicat-

laboratory procedures. In my opinion, the sedimentation test helps to complete this picture, and is a most valuable aid in the differential diagnosis of disease in the lower right quadrant.

In cases of ruptured appendix, appendical abscesses and appendicitis with generalized peritonitis much more rapid settling times were noted than in uncomplicated appendicitis, the average for such cases being 27 minutes, with variations between 19 and 39 minutes. Since normal blood counts are sometimes found in such cases, the sedimentation test is often of great value in helping to make the diagnosis.

TABLE 5.—*Gallbladder Disease*

Case	Sedimen- tation Time	White Blood Cells	Seg- mented Cells	Staf- fer Cells	Young Cells	Lym- pho- cytes	Mono- cytes	Eosino- phils	Baso- phils	Diagnosis
M. Y.	170	8,250	67	25	4	2	2	Chronic cholecystitis
B. Y.	320	9,800	74	22	2	2	..	Chronic cholecystitis
M. H.	134	8,100	79	21	Chronic cholecystitis
M. M.	100	8,900	76	19	3	..	2	(with stones)
M. M.	92	11,300	82	18	Chronic cholecystitis
M. H.	80	9,000	45	10	1	35	9	(with stones)
A. H.	180	5,200	60	40	Chronic cholecystitis
E. B.	360	7,600	39	17	1	43	Chronic cholecystitis
M. S.	10	12,600	87	11	2	Chronic cholecystitis
M. C.	27	11,200	89	11	(dental infection)
D. W.	61	9,600	46	9	..	30	11	3	1	Chronic cholecystitis
M. J.	92	9,700	36	22	2	36	4	Chronic cholecystitis
M. D.	51	10,200	66	2	..	29	1	2	..	Chronic cholecystitis
M. C.	178	8,600	56	6	..	30	6	2	..	Chronic cholecystitis
M. C. L.	58	6,300	64	2	..	33	..	1	..	Chronic cholecystitis
M. G.	120	7,400	57	1	..	36	4	1	1	Chronic cholecystitis
M. B.	127	9,125	66	30	2	2	..	(gastric ulcer)
M. S.	181	8,600	48	9	1	35	6	1	..	Chronic cholecystitis
B. R.	72	8,900	68	29	..	3	..	(with stones)
F. H.	250	8,300	68	26	5	1	..	Chronic cholecystitis
A. H.	39	13,300	52	27	4	12	4	..	1	Chronic cholecystitis
M. P.	13	17,400	53	27	2	10	7	1	..	(duodenal ulcer)
M. D.	26	15,000	77	7	..	14	2	Acute cholecystitis
										with abscess
										Acute gangrenous
										gallbladder
										Acute cholecystitis

Cholecystitis and Cholelithiasis.—The average sedimentation time in cases of chronic cholecystitis and cholelithiasis was 145 minutes, with variations between 51 and 360 minutes (table 5). In the more acute cases with fever, with or without jaundice, more rapid times (13 to 39 minutes) were noted. The presence of jaundice did not seem to make any difference in the settling rate in our cases (Linton, 1930).

Miscellaneous Conditions.—In the pyogenic infections, such as acute infection of the hand and foot, acute osteomyelitis and carbuncles, rapid sedimentation times were invariably found, the average being 24 minutes (table 6). In diabetes mellitus (with or without gangrene) there were rapid rates; on the other hand, in nephritis with nitrogen retention, there were not rapid rates, unless there was an associated

TABLE 6.—Miscellaneous Conditions

Case	Sedimen- tation Time	White Blood Cells	Seg- mented Cells	Staff Cells	Young Cells	Lym- pho- cytes	Mono- cytes	Eosino- phils	Baso- phils	Diagnosis
M. B.	11	15,800	73	21	6	Empyema
L. W.	28	13,600	60	15	5	15	5	Retropharyngeal abscess
R. S.	41	12,400	54	12	..	31	2	1	..	Mastoiditis
M. J.	16	12,000	36	35	..	23	6	Anal fistula (tuber- culous)
D. L.	30	11,000	Infected sinuses and teeth, bronchitis and mastoiditis
L. D.	18	16,200	55	16	..	29	Burns (leg)
	65	22,100	75	11	1	7	6	
M. J.	107	14,600	51	21	..	22	5	1	..	Burns (back and arms)
M. F.	233	11,700	48	5	1	42	3	1	..	Burns
M. P.	44	6,000	40	28	6	22	2	..	2	Typhoid fever
M. T.	19	8,900	29	23	2	45	1	Typhoid fever
M. H.	15	5,200	72	28	Typhoid fever
M. S.	187	11,000	55	1	..	38	1	5	..	Neurofibroma
M. P.	27	8,300	47	28	1	18	6	Intestinal obstruction
M. H.	37	10,400	52	5	2	28	10	2	1	Periostitis of man- dible
M. P.	130	7,200	68	27	4	1	..	Hemorrhoids
M. H.	96	5,800	62	38	Chronic ulcer
M. J.	257	6,500	49	9	1	37	3	1	..	Inguinal hernia
M. M.	25	9,900	82	18	Bullet wound
M. M.	126	7,000	57	6	2	35	Hernia and hydrocele
M. F.	25	13,000	42	25	12	18	3	Bacterial endocar- ditis
H. B.	154	7,300	45	19	..	32	4	Inguinal hernia
M. O.	18	15,600	81	18	1	Infected hand
M. S.	75	5,600	80	19	1	Hemorrhoids
M. L.	138	8,400	74	23	2	1	..	Postoperative hernia
M. H.	23	6,800	61	34	2	1	2	Xanthoma
M. J.	187	9,600	70	2	..	18	6	2	2	Enderteritis oblit- erans
M. W.	60	9,100	64	3	1	29	3	Cardiovascular renal disease
C. L.	83	9,900	51	2	1	37	3	6	..	Ventral hernia
M. S.	10	18,800	67	8	1	20	4	Cellulitis of leg
M. G.	45	9,600	68	26	6	Hemorrhoids
M. C.	113½	11,200	81	16	3	Infected hand
F. H.	54	8,800	76	22	2	Ulcerative colitis
B. B.	300	8,150	64	31	1	4	..	Harelip
A. B.	34	12,000	Bronchiectasis
D. L.	431	6,400	73	26	..	1	..	Dacrocystitis
C. P.	32	7,900	68	32	Postoperative hernia (infected)
C. R.	260	8,500	73	24	2	1	..	Inguinal hernia
G. H.	24	10,000	78	18	4	Diabetic gangrene
M. H.	16	11,800	39	16	10	24	11	Diabetes mellitus
M. W.	145	7,400	66	34	Chronic interstitial nephritis
R. P.	10	13,200	67	33	Diabetes mellitus
M. L.	10	10,000	40	28	1	24	4	3	..	Osteomyelitis
M. C.	30	16,900	34	44	2	18	2	Streptococcal infec- tion of leg and thigh
M. W.	23	15,400	73	12	2	9	4	Infected toe;
M. G.	30	11,300	63	7	1	22	6	1	..	lymphangitis
M. G.	44	10,200	75	3	1	19	2	Infected toe
										Lymphangitis of right leg
M. V.	103	10,200	56	2	1	34	7	Umbilical abscess
M. C.	19	13,400	51	15	2	28	3	1	..	Carbuncle of neck
M. G.	24	11,000	71	8	1	15	5	Boil—throat
M. B.	41	7,300	71	6	..	21	2	
M. A.	31	27,600	
M. C.	24	11,000	femur
M. H.	18	24,300	53	33	3	8	2	Osteomyelitis of humerus
M. D.	17	12,200	62	18	2	11	7	Gangrene of leg
M. M.	26	23,500	65	18	..	16	1	Compound Pott's fracture with osteo- myelitis
M. K.	11	12,900	72	26	2	Gangrene, endarter- itis obliterans
M. M.	23	7,450	72	22	5	1	..	Abscess thigh
M. H.	230	7,800	62	37	..	1	..	Hernia (4+ Wasser- mann reaction)
M. O.	78	7,800	62	34	2	1	..	Hernia
M. H.	20	22,200	85	13	Varicose veins
P. P.	21	9,600	61	2	2	22	4	2	..	Wound infection
										Acute streptococcal infection of throat and nephritis

active infection. In noninfectious conditions the sedimentation rates approached normal. The total leukocyte and differential counts were usually, but not always, in accord.

Malignant and Toxic Conditions.—With a few exceptions, proved cancerous conditions were accompanied by considerable acceleration of sedimentation (table 7). In fifteen of nineteen cases, the settling times

TABLE 7.—*Malignant Conditions*

Case	Sedimen- tation Time	White Blood Cells	Seg- mented Cells	Staff Cells	Young Cells	Lym- pho- cytes	Mono- cytes	Eosino- phils	Baso- phils	Diagnosis
M. H.	34	7,900	82	18	Cancer of tongue
M. S.	170	8,100	78	15	4	1	2	Cancer of antrum
M. W.	100	7,800	63	33	3	1	..	Cancer of cervix
M. W.	50	9,600	64	32	4	Cancer of cervix
R. S.	35	8,800	65	27	7	1	..	Cancer of cervix
M. W.	13	6,200	65	26	7	2	..	Cancer of vulva
M. D.	57	11,400	70	4	1	20	5	Cancer of cervix
M. C.	51	16,900	70	14	10	6	Cancer of cervix
M. B.	17	14,400	59	8	4	28	1	Cancer of cervix
M. F.	37	15,500	52	28	..	17	3	Cancer of fundus
M. L.	16	5,600	69	11	1	17	2	General carcinoma- tosis
M. R.	15	26,000	70	23	..	7	Cancer of gall- bladder
M. M.	21	15,000	61	15	5	19	Cancer of colon
M. R.	71	5,600	53	18	..	23	2	2	2	Cancer of breast
M. B.	24	5,600	73	2	..	21	4	Cancer of breast
B. B.	62	8,900	77	7	..	16	Cancer of stomach
M. C.	372	10,400	62	8	1	25	2	2	..	Cancer of submaxil- lary gland
S. C.	84	7,000	51	7	..	38	4	Cancer of intestine
M. S.	130	10,700	Cancer of rectum

TABLE 8.—*Goiters*

Case	Sedimen- tation Time	White Blood Cells	Seg- mented Cells	Staff Cells	Young Cells	Lym- pho- cytes	Mono- cytes	Eosino- phils	Baso- phils	Basal Metabolic Rate
E. R.	440	7,200	68	28	3	..	1	+39 to +43
M. F.	125	7,200	36	27	..	29	3	5	..	-12 to 0
M. B.	220	12,200	76	24	+45
M. C.	355	7,600	68	26	4	2	..	-13 to 0
M. C.	165	7,800	63	37	+54
M. E.	98	6,100	71	24	4	1	..	+7
M. T.	120	13,400	66	10	4	18	..	2	..	+90 to +100
M. G.	152	9,400	69	28	2	1	..	+40 to +52
E. D.	150	8,000	72	24	4	+56 to +61

were between 13 and 71 minutes, with an average of 39 minutes. In the other four, the rates were between 100 and 372 minutes, the latter rate occurring in a case of recurrent submaxillary tumor with no signs of cachectic absorption.

In cases of toxic thyroid, on the other hand, there was little or no acceleration of the sedimentation rate, the average being 208 minutes with variations between 120 and 440 minutes (table 8). It would seem, therefore, that the toxins of infections and malignant conditions produce changes in the blood plasma that permit an accelerated sedimentation time, while the endocrine secretions, normal or abnormal, have no

such effect (Mora and Gault, 1930; Hufschmid, 1930). This brings up the question of the mechanisms responsible for the differences in settling time in health and in certain disease conditions.

MECHANISMS INVOLVED IN THE SEDIMENTATION TEST

Various attempts have been made to explain the variation in the sedimentation time. One of the most popular theories has to do with the electric charge of the erythrocytes (Fahraeus, 1918; Hüber, 1920; Linzenmeier, 1922; Friedlaender, 1924; Baer and Reis, 1926; de Haan, 1918; Plaut, 1920). Hüber, using a glass tube filled with diluted normal blood, with one end attached to a positive and the other to a negative electrode, demonstrated that the erythrocytes migrated toward the anode, indicating that they themselves carry a negative charge. According to this theory, in normal blood the erythrocytes carrying similar charges repel each other so that they remain separated by uniform distances and do not clump. Anything that tends to remove the electric charge of the red cells will allow them to clump and settle more rapidly in their plasma. Since erythrocytes of normal blood, transferred to the plasma of blood under inflammatory conditions, settle more quickly than in their own plasma, the bodies causing the electrical discharge must be in the plasma. According to some writers (Clausser, 1923; Fahraeus, 1917; Hüber, 1920; Nees, 1925; Schurer and Eimer, 1921), the plasma of such abnormal blood contains positively charged agglutinins which neutralize the negative charge of the red cells, while others (Solomon, 1925; Vorschütz, 1924; von Oettingen, 1922) believed that such plasma contains increased globulins which increase the viscosity and decrease the negative charge of the erythrocytes. J. Müller (1844), C. G. Lehmann (1853) and H. A. Reimann (1931) also expressed the belief that the variation in sedimentation time depended on the abnormal viscosity of the plasma and the agglutination of the red cells in various infectious diseases. Groedel and Hubert (1925), on the other hand, found no parallelism between the speed of sedimentation and the viscosity of the plasma. Kürsten expressed the belief that an abnormal proportion of blood cholesterol to lecithin accounts for the disturbance in the suspension stability of the erythrocytes. Although the electric theory makes an excellent working hypothesis, there is no direct proof of its correctness, except perhaps the fact that the red cells do carry a negative charge.

The differences of opinion as to the relation of the viscosity of the plasma to the sedimentation time led us to make parallel viscosity and sedimentation tests on a group of one hundred patients to see whether there was any consistent relationship. Numerous difficulties were encountered in developing a satisfactory method for determining the viscosity of blood plasma with sufficient accuracy to make the readings valuable. At first, determinations were made on the Hess viscosimeter,

but owing to the small caliber of the capillary tubes, it was found impossible to keep them clean enough to prevent "crawling." The variations due to this as well as to other imperfections in the machine were greater than those between the different plasmas, making the results valueless. It was finally decided to use the Ostwald type of viscosimeter, which has a larger capillary tube and depends on gravity for its flow. After numerous experiments, a small tube was made which could be used with as little as 4 cc. of plasma. Since variations in temperature markedly affect the viscosity of fluids, it was decided to make these tests in a water bath of constant temperature (25 C.). Also, since the viscosity of plasma increases after exercise (Sahli) and after the taking of food, these tests were made in the morning before breakfast, with the patient in bed. Dr. F. Lowell Dunn, director of the department of clinical research, College of Medicine, University of Nebraska, gave his personal assistance and the use of equipment in this work.

TECHNIC

The following technic was used: About 12 cc. of blood was taken from a vein in the usual manner and placed in a centrifuge tube containing 40 mg. of potassium oxalate or 2 mg. of heparin to prevent coagulation (Rourke and Plass, 1929). The tube was centrifugated until the clear plasma remained on top. This was separated with a pipet and 4 cc. introduced into the arm, *CD*, of the viscosity tube (fig. 1), which was suspended in a water bath at 25 C. The plasma was then drawn up through the tube, *AB*, by suction until the meniscus was above the line *O*. It was then allowed to settle by gravity and the time required for it to pass from *O* to *P* determined by a stop-watch. A similar determination was made in the same tube, fresh distilled water being used instead of plasma, and the viscosity of the plasma then being expressed in relation to that of water, thus: settling time for plasma divided by settling time for water equals viscosity of plasma. The tests for sedimentation of the blood were made in the manner previously described.

RELATION OF THE SEDIMENTATION TIME TO THE VISCOSITY OF THE PLASMA

A tabulation of the results shows a definite relationship between the sedimentation time of the blood and the viscosity of the plasma. At first thought, one would expect to find a direct relationship, that is: the greater the viscosity, the slower the settling time, and vice versa. Actually, the reverse was found to be true; the greater the viscosity, the more rapid the settling time, and vice versa. However, this is not a 1:1 relationship, and is best expressed by a graph (fig. 2). The curve obtained shows a sudden fall of viscosity from 0 to 30 minutes, a gradual fall from 30 to 130 minutes and a slow flattening out from 130 minutes to the normal ranges. Apparently, some new element is introduced in plasmas with settling times of 30 minutes or less which gives a sudden increase in viscosity in this range—an element that is either absent

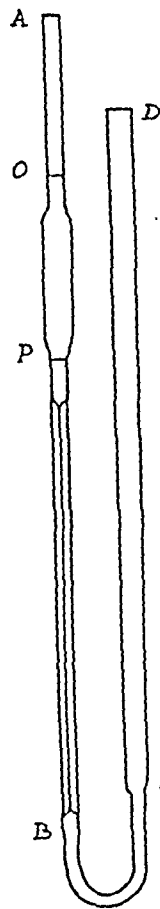


Fig. 1.—Tube in which viscosity of the blood plasma was tested. Four cubic centimeters was introduced into the arm, *CD*, which was suspended in a water bath. The plasma was then drawn up through the tube *AB* by suction until the meniscus was above the line *O*. The time required for it to pass from *O* to *P* was determined by a stop-watch.

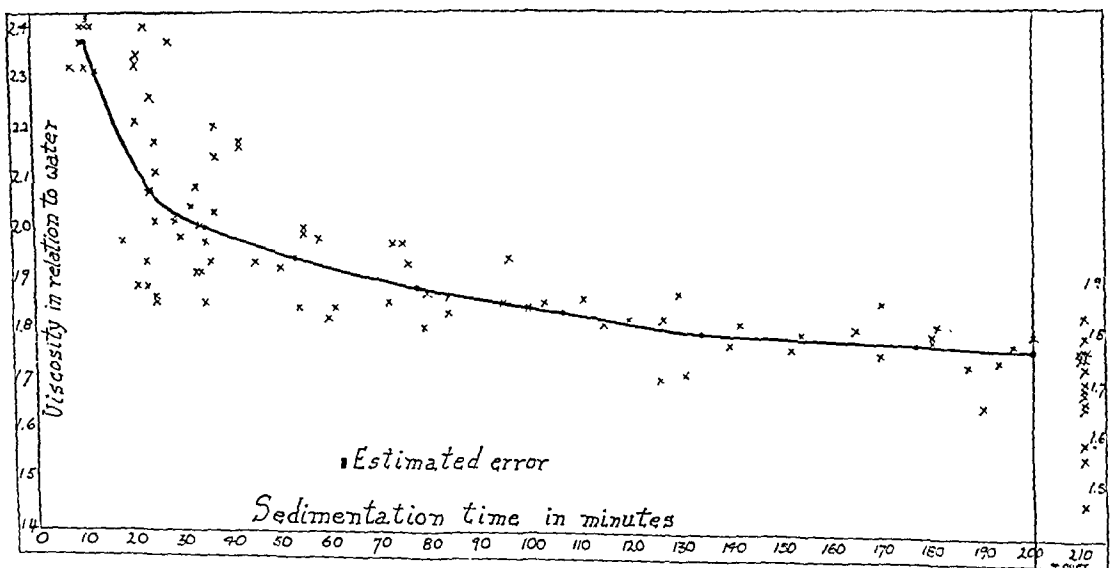


Fig. 2.—Chart showing the relation between the increase in viscosity of the plasma and the sedimentation time of the blood.

or present in a much lower degree in plasmas with sedimentation rates over 30 minutes. Whether there is a cause and effect relationship between the sedimentation time of the blood and the viscosity of the plasma or whether they are both the result of still another factor is a matter of conjecture. With the thought that the increase in viscosity in plasma of infected patients was possibly due to increase in nitrogen compounds (split proteins, etc.), several total nitrogen determinations were made by microchemical methods, with the personal assistance and advice of Dr. Meyer Beber, associate professor of biochemistry, College of Medicine, University of Nebraska (Jones, 1929; Westergren, 1931). However, the variation between plasmas were within the limits of error, as well as within the limits of normal, and without consistent tendency, so that no definite conclusions could be drawn. In addition, as previously noted, cases of nitrogen retention do not show accelerated sedimentation times or increased viscosity, unless they are associated with active infection. In diabetes mellitus, there are an acceleration of the sedimentation time and an increased viscosity, but increases in blood sugar could explain only a small percentage of the total cases in which there were rapid settling times.

On the other hand, the increase in viscosity (and possibly the acceleration of the sedimentation rate) may be due to an increase in or a change in the form of the lipoid content of the plasma. This suggests a theory based on changes similar to those that take place in fixed tissue cells during inflammation and necrosis: namely, a withdrawal of fat from its normal, finely divided state of emulsion into one involving larger particles, finally leading to coagulation necrosis and disintegration. That a similar process may take place in the plasma is not inconceivable. At first this may be of slight degree (gradual curve) and then, at a certain stage, rather suddenly increase in amount, giving the type of curve found in figure 2. If one favors the electric theory as a cause of the acceleration in sedimentation time, one has only to assume that the disturbance in plasma content, and therefore viscosity, causes a discharge of the negatively charged erythrocytes, allowing them to clump and fall more rapidly. However this is only a theory, since the only direct evidence is the negative charge carried normally by the erythrocytes and the increase in viscosity of plasmas with rapid sedimentation rates. The rest must be filled in by deduction until further direct evidence is available.

SUMMARY AND CONCLUSIONS

1. The blood sedimentation test is a simple and reliable means of diagnosis and prognosis in general surgical conditions, often surpassing the blood count in value.

2. It is of particular value in the differential diagnosis of appendicitis from other pathologic conditions of the lower right quadrant of the abdomen.

3. There is an inverse relationship between the settling time of the erythrocytes and the viscosity of the plasma, which is best expressed by a graph.

4. It is suggested that variations in viscosity may be due to variations in amount or change of form of the lipid content of the plasma.

5. On this basis, a theory is offered to explain the variations in sedimentation time, which embraces the electric theory advanced by other workers. However, the exact mechanism is still unknown, and further work along this line seems indicated.

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STUDIES OF THE PHYSIOLOGY OF THE LIVER

XXII. THE VAN DEN BERGH REACTION IN THE JAUNDICE FOLLOWING COMPLETE REMOVAL OF THE LIVER*

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The method of estimating bilirubin in the blood that was introduced by Hijmans van den Bergh is extensively used in clinical medicine. It differs from other methods of estimating bilirubin in blood serum or plasma since it not only allows quantitative estimation of bilirubin, but reveals qualitative differences by which jaundice of hemolytic and obstructive origin can be differentiated. Van den Bergh rediscovered the color reaction given by bilirubin with the diazo reagent of Ehrlich, and applied this reaction in producing an accurate test for small amounts of bilirubin in small amounts of serum. With regard to the delicacy of the test, he found that a solution of 1:1,500,000 of pure bilirubin dissolved in alcohol still affords a positive result. Next he made the original and significant observation that in some cases of jaundice it is unnecessary to bring the bilirubin into alcoholic solution, but that a positive coupling with production of the azo-dye can be obtained by adding the diazo reagent direct to the icteric serum. In this way he was able to divide icteric serums into two groups: (1) those that gave a color reaction at once (maximal within thirty seconds) on the addition of the diazo reagent directly to the serum (van den Bergh's prompt direct reaction), and (2) those that did not give a color reaction or gave it only after long delay on the addition of the diazo reagent direct to the serum (van den Bergh's delayed direct reaction).

Every icteric serum gives an immediate color reaction with the diazo reagent after precipitation with alcohol so as to bring the bile pigment into alcoholic solution. The application of this method is known as van den Bergh's indirect reaction. Since serums of group 2 (delayed direct reaction) are usually subjected to this test, they are often referred to as giving an indirect reaction as opposed to serums of group 1 (prompt direct reaction); they give immediate color with the diazo reagent whether or not alcohol has been added to the serum.

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* From the Division of Experimental Surgery and Pathology, the Mayo Foundation.

In correlating the recent investigations concerning the origin and excretion of bile pigment, Rolleston and McNee¹ developed a theory of jaundice. The basis of their views is that the polygonal cells of the liver are not essentially concerned with the manufacture of bile pigment, but with its transference from the vascular capillaries into the bile canaliculi. The view was also put forward that the cells of the reticulo-endothelial system, those in the spleen and other lymphoid tissue, those in the bone marrow and also the Kupffer cells of the liver deal with the breaking down of hemoglobin and the formation of bile pigment. As a result of the differences in the van den Bergh reaction in different types of jaundice, Rolleston and McNee suggested that in its passage from the vascular capillaries through the hepatic cells, bilirubin is modified in some unknown way. On these hypothetic views, icterus, defined as bilirubinemia, might arise in several ways:

1. When bile pigment, formed in the reticulo-endothelial cells, passes through the hepatic cells to reach the bile canaliculi, it is obstructed in its outflow and finally reabsorbed into the blood.

2. When, owing to injury and functional derangement of the polygonal cells, the bile pigment from the endothelial cells is unable to enter them, it must pass instead directly into the hepatic veins and so accumulate in the general circulation. A second mechanism arising in a similar manner might occur in excessive destruction of blood during which more bilirubin is formed in the reticulo-endothelial cells than the cells of the liver can excrete. In such circumstances some bile pigment might pass normally through the hepatic cells into the biliary passages, the excess going directly into the hepatic veins.

3. When, besides the injury of the polygonal cells, some obstruction is present in the biliary passages, some bilirubin passes directly into the hepatic veins, and some through polygonal cells which are still functioning, to be obstructed in the biliary passage and then absorbed.

The experimental work that furnishes the basis of the foregoing theory of jaundice is summarized in our previous studies regarding the formation of bile pigment.² Mann, Bollman and Magath,³ in 1924, described a yellow pigment which progressively accumulates in the urine, plasma and fatty tissues following total removal of the liver from dogs.

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It was usually noted in the urine a few hours after hepatectomy, and appeared in the plasma in from three to six hours after operation. In about sixteen hours a definite icteric tint of the sclera could be noted. At necropsy all the fatty tissue of the body was a dirty yellow. This yellow pigment gave all the chemical reactions for bilirubin. The yellow serum gave the delayed van den Bergh reaction, and the pigment could be extracted by chloroform from the plasma and also from the tissues. The formation of this pigment did not depend on any of the intra-abdominal organs. Its rate of development under certain conditions was accelerated by the intravenous injection of laked blood. From these studies, it appeared that a high percentage of the bile pigment excreted by the liver is of extrahepatic origin.

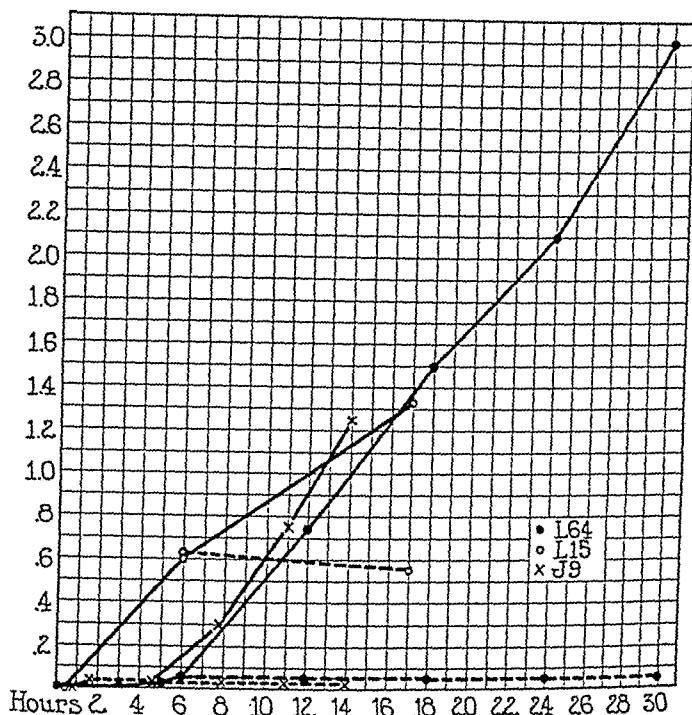
In all our experiments on complete removal of the liver it has been noted that the bilirubin that accumulates in the blood and tissues is comparable to that found in man normally and in cases of hemolytic icterus; that is, the indirect van den Bergh reaction is positive but the direct reaction does not occur. The pigment is soluble in fat and may be extracted from fat tissue or blood by chloroform. One marked difference is present, however; the dog's kidney excretes this indirect-reacting bile pigment as soon as quantities sufficient to give a faint reaction (0.05 mg. per hundred cubic centimeters of blood) are present in the blood. This bile pigment in the dog's urine gives the prompt direct reaction and, as far as we can determine, is identical with the bile pigment in the urine of obstructive jaundice. This fact does not appear to be due to a difference in the nature of the serum bilirubin in the two species as it may depend on the renal threshold of bilirubin of this type. The level of serum bilirubin in man is normally more than ten times that in the dog, and it is probable that the kidney of man would be correspondingly less sensitive to increased amounts of this indirect-reacting bilirubin in the blood. The kidney of man also has a threshold for the direct-reacting bilirubin of obstructive jaundice, but this is not high compared with indirect-reacting bilirubin.

Because we had found that indirect-reacting bilirubin of the blood of hepatectomized dogs became direct-reacting after it passed through the kidneys, it appeared probable that the direct-reacting bilirubin in the blood might be bilirubin that had passed through the cells of the liver. This concept is by no means new, as van den Bergh mentioned in his original article that the reaction of pigment in bile was direct when only the indirect reaction was obtained in the blood.

Direct experimental proof of the passage of bilirubin from the blood to the cells of the liver and into the blood again is lacking. It appears possible that the direct reaction for bilirubin in blood may be due to the retention of some other substance in addition to the bilirubin

in the blood in obstructive jaundice. Accordingly, we attempted to cause the accumulation of bilirubin in the blood, some of which may have passed through the hepatic cells, and part of which could not have done so. If the liver were adding some other substance to the blood to produce the direct reaction, it seems unlikely that this substance would be identical in amount with the bile pigment added.

In these experiments obstructive jaundice was produced by double ligature, section of the common bile duct and removal of the gallbladder with aseptic technic and ether anesthesia. In some experiments the anesthesia was continued for an hour, at which time complete removal of the liver was accomplished by a method previously described. The



Curves showing increases of indirect-reacting serum bilirubin following removal of the liver and the lack of change in the direct-reacting serum bilirubin present at the time of hepatectomy because of previous biliary obstruction. Time is counted in hours from the moment of ligation of the common bile duct and extirpation of the gallbladder. Indirect-reacting serum bilirubin is represented in milligrams per hundred cubic centimeters of blood by the solid line and direct-reacting serum bilirubin by the broken line. In animals L64 and L15, the liver was removed six hours after ligation of the common bile duct. In animal J9, hepatectomy was performed ninety minutes after biliary obstruction.

animal was allowed to recover from the anesthetic, and dextrose was administered intravenously at hourly intervals in amounts sufficient to maintain an approximately normal level of sugar in the blood. Blood was withdrawn by direct venipuncture at hourly intervals throughout the course of the experiments, and estimations of serum bilirubin were

made by the quantitative method, both direct and indirect van den Bergh tests. In other experiments ligation of the common bile duct was accomplished and the animal was allowed to recover from the anesthetic for six hours; then hepatectomy was performed under ether anesthesia, with subsequent recovery and administration of dextrose.

The results of these experiments were conclusive with respect to the relation of the liver to the nature of the van den Bergh reaction in the blood. Within a short time after ligation of the common bile duct and extirpation of the gallbladder, the direct reaction showed the same amount of bilirubin present as the indirect reaction, and both increased with the time after operation. Subsequent hepatectomy, regardless of the level of serum bilirubin, was followed by a continued rise in the indirect-reacting serum bilirubin, but the direct-reacting bilirubin remained at the same value it had reached because of the biliary obstruction, and no increase occurred in this direct-reacting bile pigment. The removal of the liver a short time after ligation of the common bile duct or several hours later, the direct-reacting serum bilirubin being present in traces or in fairly large amounts, gave identical results. There were no exceptions to this observation; although certain variations occurred in different animals, these variations did not influence the nature of the van den Bergh reaction. The rate of accumulation of bile pigment in the blood proceeds uniformly for several hours after ligation of the common bile duct in any given animal, but this rate may be markedly different in other animals. In a few animals a definite decrease of the serum bilirubin occurred following the administration of the anesthetic (ether) for the second operation. When this occurred, the total bilirubin content of the serum was found to be decreased so that the relationship of the direct-reacting to the indirect-reacting pigment was not disturbed.

That the bile pigment that accumulates in the blood following biliary obstruction passes from the blood probably through the hepatic cells into the lymph and also probably directly into the blood may be illustrated by the following experiment: Under ether anesthesia the thoracic duct of a dog was exposed, a cannula was inserted, and the cystic duct and common bile duct were ligated. In less than fifteen minutes the lymph from the thoracic duct, which had previously been colorless, became definitely yellow, and within thirty minutes a definite direct van den Bergh reaction was obtained. Not until two hours after ligation did the serum in this animal show a yellow tinge, and a positive direct reaction was not obtained until three hours had elapsed. At this time the bilirubin concentration was 0.8 mg. per hundred cubic centimeters and the reaction was direct in the lymph; there was a trace only of bilirubin in the blood. After five hours the blood had 0.1 mg. of bilirubin per hundred cubic centimeters, and the reaction was direct;

the lymph had 0.4 mg., and the reaction was direct. This experiment, however, should not be taken as proof that all the bilirubin of the blood, after obstruction of the biliary outflow, has passed through the lymphatics. In five hours less than 100 cc. of lymph represented the entire flow from the thoracic duct, and the bile pigment could be much more concentrated than in the volumes of blood that had passed through the liver during the same period.

The total blood volume of the animal was more than 1,600 cc., and the entire amount of bile pigment removed in the lymph during the period of the experiment could be added to this volume of blood without giving more than a trace when tested. Since the blood contained more than a trace of bilirubin, it is obvious that some direct-reacting bilirubin had been added to the blood.

It should also be noted that the conversion of the indirect-reacting bilirubin of the blood to the direct-reacting bilirubin is not specific for the liver, since the kidney of the dog is able to excrete urine containing direct-reacting bile pigment when only the indirect-reacting pigment is present in the blood after hepatectomy.

SUMMARY

The serum bilirubin that gives the prompt direct van den Bergh reaction following ligation of the common bile duct of animals is unaltered by subsequent complete removal of the liver. The bile pigment that continues to accumulate in the blood following removal of the liver gives only the indirect van den Bergh reaction and is not altered by the presence of direct-reacting bilirubin in the blood. For this reason bilirubin of the blood that does not give the direct van den Bergh reaction may be considered to be of extrahepatic origin and as not having passed through hepatic cells. The direct reaction of bile pigment in the blood is evidence of the reabsorption of bilirubin from hepatic cells and is not dependent on the original site of formation of bilirubin. The liver appears to be actively concerned in the withdrawal of bilirubin that gives only the indirect reaction from the blood, and in the conversion of this complex bilirubin to the simple bilirubin that gives the direct van den Bergh reaction.

TRANSPHRENIC SPREAD OF DISEASE

WITH REPORTS OF SIX CASES *

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Transphrenic spread of disease has received scant attention in the literature. Beye¹ reported ten cases of transphrenic spread of infection. In nine cases, the extension was from a secondary subphrenic abscess to the thorax, and in seven of these there was a spontaneous or operative defect in the diaphragm. In the tenth case, the spread was from the thorax to the abdomen. In Beye's opinion, the primary lesion began in the appendix four times, in peptic ulcers four times, as a perinephric abscess once, and as acute empyema once. He concluded that extension upward from a subphrenic abscess is not uncommon, but that extension downward from empyema is infrequent. This extension of infection through the diaphragm is sufficiently common to be mentioned in a number of standard textbooks as a complication of empyema and subphrenic abscess. Pratt,² quoting Robson and Moynihan, mentioned the finding of fat necroses in the pericardium in a case of acute hemorrhagic pancreatitis. Little prominence has been given to the transphrenic spread of tuberculosis and cancer, probably because of the frequency with which these diseases are widely disseminated.

In the 160 consecutive autopsies performed at the University of Virginia Hospital during the year ending July 1, 1931, transphrenic spread of disease occurred six times, an incidence of 3.75 per cent. Three of the cases were consecutive. The transphrenic spread occurred as a complication of the following conditions in the order of presentation: (1) peritonitis and subphrenic abscess following intussusception; (2) subphrenic abscesses following perforation of a gastric ulcer; (3) generalized tuberculous peritonitis with marked subphrenic involvement; (4) acute hemorrhagic pancreatitis; (5) primary carcinoma of the head of the pancreas with spread to the under surface of the diaphragm; (6) type I pneumococcus pericarditis and bilateral empyema.

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1. Beye, H. L.: Transphrenic Infection, *Arch. Surg.* **14**:240 (Jan.) 1927.

2. Pratt, J. H.: *Diseases of the Pancreas*, Oxford System of Medicine, New York, Oxford University Press, 1920, vol. 3, p. 492.

The pathways by which disease may extend through the diaphragm and the probable location of resulting secondary lesions may be anticipated with some degree of accuracy since the work of Lemon, Higgins and Graham,³ who studied, in dogs, the lymphatic circulation of the diaphragm by means of intraperitoneal, intrapleural and intrapericardial injections of finely particulate graphite suspensions. They concluded in part:

1. Particulate matter injected into the peritoneum is taken up diffusely on the under surface of the diaphragm and appears in the rich subpleural plexus of lymphatic vessels in from three to five minutes.

2. From this subpleural plexus the following five main channels carry the particulate matter through the thoracic or retroperitoneal lymphatics into the blood stream, in from thirty to ninety minutes:

(a) Eighty per cent is carried by the so-called sternal route from sternal, costal and lumbar portions of the diaphragm to the parasternal lymph nodes in the second interspace by way of three or four channels which parallel the internal mammary vessels.

(b) Next in importance is the pulmonary route, which arises from more central portions of the diaphragm and drains into the paratracheal and parabronchial nodes by way of channels along the phrenic nerves (between the pericardium and pleura), esophagus and pulmonary mesentery.

Efferent trunks from the sternal, paratracheal, and parabronchial nodes empty directly or indirectly into the right lymphatic or the thoracic ducts near their venous confluences.

(c) A third and less important route arises from the vault and posterior portions of the diaphragm and courses cephalad along the posterior thoracic wall into the thoracic duct at various levels.

(d) Vessels comprising the fourth and fifth routes also arise from the vault and posterior parts of the diaphragm, but they then head downward through the diaphragm into the perirenal and peripancreatic nodes, respectively, both of which drain into the receptaculum chyli.

3. There is a vessel on each side which arises in and descends down the posterior thoracic wall to the perirenal nodes which sometimes receives tributaries from those portions of the diaphragm (2d) which give rise to the fourth and fifth routes.

4. Injections of particulate matter into the pleura were followed by its appearance in the perirenal nodes, probably by absorption into the posterior descending thoracic trunks. There was no evidence of absorption into the diaphragmatic or visceral pleura. (Their studies of intrapleural and intrapericardial injections, however, were not complete.)

5. The lymphatics on the right side are larger and carry a larger proportion of particulate matter than those on the left.

6. Paralysis of the diaphragm interferes with the speed of transmission from the peritoneum to the blood stream through the diaphragm.

3. Lemon, W. S., and Higgins, G. M.: Lymphatic Absorption of Particulate Matter Through Normal and Paralyzed Diaphragm: Experimental Study, *Am. J. M. Sc.* **178**:536 (Oct.) 1929. Higgins, G. M., and Graham, A. S.: Absorption from Peritoneal Cavity, with Especial Reference to Diaphragm, *Proc. Staff Meet., Mayo Clin.* **4**:9 (Jan. 9) 1929.

REPORT OF CASES

CASE 1.—*History*.—The patient, M. C., a white girl, 13 years old, on admission to the hospital had intestinal obstruction of five days' duration. Operation disclosed a Meckel's diverticulum that had intussuscepted into the ileum, several perforations of the intestine and generalized peritonitis. Râles were reported in the base of the left lung six days after operation. They did not persist. The patient died three weeks after operation.

Autopsy.—Autopsy disclosed generalized peritonitis with subdiaphragmatic abscess in the region of the left lobe of the liver, the stomach, the spleen and the left half of the transverse colon. The base of the left lung was adherent to the diaphragm by a thick fibrinopurulent exudate. There was no gross defect in the diaphragm. There was an eroding substernal abscess about 2 cm. in diameter at the level of the third ribs. Other findings were not revelant.

The primary lesion was an intussusception, which led to generalized peritonitis and subphrenic abscess. From this there was, apparently, direct lymphatic transphrenic spread of the purulent infection to the left diaphragmatic and visceral pleura and further lymphatic spread by the sternal route to the substernal glands, which became abscessed.

CASE 2.—*History*.—The patient, C. D., a white man, aged 48, was stuporous when admitted to the hospital. He had been ill for two months with increasing nausea, vomiting, loss of weight and strength, fever and the frequent passage of tarry stools. He was given infusions and transfusions in an effort to prepare him for operation. Sixteen and eighteen days, respectively, after admission 750 and 150 cc. of sterile, slightly cloudy fluid containing many polymorphonuclears were aspirated from the right pleural cavity. Four days later, a diagnosis of subphrenic abscess following perforated peptic ulcer was made, after pus was aspirated from the sixth right interspace. Operation, performed an hour later, showed the visceral and parietal pleura adherent over a large subphrenic abscess, which was drained. The patient had profuse intestinal hemorrhages on the fourth, fifth and sixth days after operation and died.

Autopsy.—A large gastric ulcer, with a freshly thrombosed artery projecting from the crater and numerous friable perigastric adhesions, was adherent to the anterior edge of the liver, straddling the suspensory ligament. Adherent nearby structures had walled off a subphrenic abscess on each side of the suspensory ligament. The abscess on the right had been drained. The one on the left had not been entered. The intestine was filled with old blood. There was diffuse cellulitis of the diaphragm, which, however, was intact, save for the operative drainage tract.

The base of the right lung was adherent. There were two separate empyema sacs in the right pleural space. One was just above the transpleural drainage tract, the other was at the extreme apex. The right tracheobronchial lymph glands were enlarged and acutely inflamed. The pericardium, which was adherent to the right lung, contained about 200 cc. of slightly cloudy fluid. Other findings were of no interest.

A bleeding and perforated gastric ulcer caused two separate subphrenic abscesses, from which there was apparently direct lymphatic transphrenic spread to the right diaphragmatic pleura, with subsequent empyema formation. There was, perhaps, further lymphatic spread

by the pulmonary route between the pleura and pericardium to the right tracheobronchial lymph glands, with consequent pleuropericardial adhesions and pericardial fluid. It is possible that the pneumonia in the middle lobe was the cause of the enlargement of these glands, and that an extension of the empyema caused the pericardial adhesions and fluid. As twelve days elapsed between the discovery of polymorphonuclears in the chest fluid and the finding of a small area of gray pneumonia at autopsy, it is unlikely that either of the two empyema sacs followed the pneumonia.

CASE 3.—History.—The patient, C. M., a colored woman, aged 28, married, was admitted to the hospital with tuberculous peritonitis of about five months' duration. There was no evidence of pulmonary or pleural involvement. An exploratory laparotomy was performed and both tubes removed, because they seemed to be the primary focus of the generalized tuberculous peritonitis. The patient survived the operation seventeen days.

Autopsy.—Autopsy revealed diffuse tuberculous peritonitis with multiple tubercles, heavy fibrinous adhesions between all abdominal viscera, about 1,000 cc. of slightly turbid fluid and a large collection of fibrinous exudate between the diaphragm and the liver. There was diffuse tuberculous endometritis. There was early miliary tuberculosis of both layers of the right pleura, with about 1,000 cc. of nearly clear straw-colored fluid. There were a few discrete tubercles on the left diaphragmatic pleura. There was no evidence of pulmonary or tracheobronchial glandular tuberculosis. Other findings were irrelevant.

Primary tuberculosis of the pelvic viscera was followed by subphrenic tuberculosis, which apparently spread through the lymphatics across the diaphragm to both pleural surfaces. Quantitatively, the transphrenic spread was much greater on the right side than on the left. There was no evidence of tuberculosis in the lungs or in the tracheobronchial glands.

CASE 4.—History.—The patient, P. H., a white man, aged 40, was admitted to the hospital with severe generalized abdominal pain and distention of three days' duration. He had previously had several attacks of abdominal pain which had been attributed to gallbladder disease. A diagnosis of peritonitis was made, but the patient was thought to be too ill to stand immediate operation. He died a few hours after admission.

Autopsy.—Autopsy revealed acute diffuse serosanguinofibrinous peritonitis with multiple fat necroses, more abundant in the omentum and mesentery, and marked acute hemorrhagic pancreatitis and peripancreatitis. The gallbladder was of the strawberry type and contained a single cholesterol stone. There was no evidence of obstruction in the common bile or pancreatic ducts. There were a few areas of fat necrosis on the pleural surface of the left vault of the diaphragm. Other findings were not interesting.

This is a case of transphrenic spread of pancreatic ferments with fat necroses in the left diaphragmatic pleura following acute hemorrhagic pancreatitis.

CASE 5.—*History*.—The patient, C. B., a white widow, aged 71, was admitted to the hospital with ascites and signs of fluid in the left pleural cavity. Exploration confirmed the preoperative diagnosis of generalized abdominal carcinomatosis. The primary focus was not determined. The patient died three days after operation, with symptoms of acute intestinal obstruction.

Autopsy.—Autopsy disclosed extensive generalized abdominal carcinomatosis with ascites. There were two metastases in the left lobe of the liver. The left peritoneal surface of the diaphragm was covered with cancer nodules. The primary cancer was in the head of the pancreas.

The left parietal pleura was studded with metastases, which were more numerous over the diaphragm. There was an exudate of about 1,000 cc. of clear fluid. There were a few metastases in the parietal pericardium and a slight increase in pericardial fluid. No other metastases were found.

In this case primary carcinoma in the head of the pancreas gave rise to metastases on the left peritoneal surface of the diaphragm. Apparently, there was then a direct transphrenic lymphatic spread of carcinoma, with secondary carcinomatosis of the left parietal pleura and the parietal pericardium. It is possible that some of the pericardial metastases were carried by the pulmonary route between the parietal pericardium and the pleura. There was no evidence of metastases to the tracheobronchial glands or to the parenchyma of the lungs.

CASE 6.—*History*.—The patient, H. W. F., a white man, aged 37, was admitted to the hospital almost moribund with acute congestive failure and fever. He had been well, except for occasional attacks of asthma until he contracted an acute respiratory infection nineteen days before admission. Fever and asthma lasted for four or five days. In the next two weeks there were several short attacks of orthopnea and dyspnea followed by edema of the extremities. Soon after admission, the patient was found to have pulsus paradoxus. Type I pneumococcus pus was aspirated from the right pleura and the pericardium. Culture of the blood gave positive results for type I pneumococcus. There were also signs of fluid in the left pleural space. Pericardiostomy was done and about 1,000 cc. of pus was evacuated. The empyema pocket on the right side was aspirated several times. The patient died two days after operation.

Autopsy.—Autopsy disclosed bilateral posterior basal empyema, acute purulent pericarditis with surgical drainage, acute diffuse mediastinitis with small abscesses at the upper anterior pericardial reflection and in the fourth left interspace near the sternum, and acutely inflamed right parabronchial glands. There was an area of gray pneumonia in the upper lobe of the left lung. The left empyema sac appeared to be the result of direct extension from the pericardium. Microscopically, the lung showed red, gray, resolving, unresolved and organizing pneumonia. There were four or five pea-sized abscesses around the tail of the pancreas. There were several small infarcts in the upper pole of the left kidney with multiple microscopic venous thrombi. There was no other evidence of infection.

This case is included, in spite of the pneumococcus septicemia and the multiple infarcts in the left kidney, because the abscesses around the tail of the pancreas seem to illustrate transphrenic spread of infection from the pleura by the posterior thoracic vessels which anastomose

with those of the fifth route, which in turn lead from the posterior thoracic surface of the diaphragm to the peripancreatic nodes. Or, perhaps, the infection invaded directly those vessels of the fifth route that arise beneath the diaphragmatic pericardium.

SUMMARY

Six cases of transphrenic spread of disease are presented. In only one case (case 6), did the process originate above the diaphragm. In each of the other cases the primary lesion was in the abdomen, and transphrenic spread occurred directly from the under surface of the diaphragm, which was secondarily involved by cancer once (case 5), by acute hemorrhagic pancreatitis once (case 4), by tuberculosis once (case 3) and by pyogenic infections twice (cases 1 and 2).

The spread was from the left subphrenic region to the left pleura in three cases, from the right subphrenic region to the right pleura in one case, from the right subphrenic region to both pleurae in one case and from both pleurae and the pericardium to the region of the tail of the pancreas in one case. In one case (case 3), the spread seemed to be quantitatively much greater on the right than on the left. This is in accord with the experimental data (conclusion 5). Oddly enough, in half of this group of cases the transphrenic spread occurred only on the left.

Of the five pathways described by Lemon, Higgins, and Graham² by which lymph drains from the diaphragm, the sternal route was apparently illustrated once, the pulmonary route twice, and the fifth route, leading to the peripancreatic region, once. Simple spread from peritoneum to pleura occurred five times.

It seems desirable to be mindful of the probability of transphrenic spread of intrathoracic or intra-abdominal disease. In order to anticipate some of the seemingly bizarre locations of the secondary transphrenic lesions, it is necessary to know the various routes by which materials reaching the rich diaphragmatic lymphatic plexus are transported to the blood stream.

A REVIEW OF UROLOGIC SURGERY

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BLADDER

Tumors.—Cunningham²¹ stated that the growth of neoplasms of the bladder, either benign or malignant, although variable, may be quite rapid; he cited 2 highly malignant cases in which the neoplasms attained considerable size, one within nine weeks and the other within six months.

In a consideration of whether misbehaved cells of the bladder which produce benign tumors may subsequently become malignantly active, Bumpus stated that this change was never observed at the Mayo Clinic, and both Cunningham and Bumpus believe that tumors of the bladder are either benign or malignant from their inception. The disagreement on this subject is substantiated by much evidence. Ewing stated that recurrence of benign tumor usually represents development of new growths from preexisting lesions and such recurrence is not an implantation of the old growth. Recurrent malignant tumors are more likely to be the result of retained cell groups in the submucosa. Nevertheless, recurrence of benign tumors is common, and occasionally malignant tumors are discovered in bladders in which benign tumors have been present. In the examination at necropsy of 132 cases of malignant tumor of the bladder at the Mayo Clinic, metastasis was found in 40 (30.3 per cent). Geraghty found metastasis at necropsy in 68 (32.2 per cent) of 219 cases of carcinoma of the bladder at Johns Hopkins Hospital. Of a total of 411 cases of malignant tumors of the bladder reviewed from various sources, necropsy revealed gross metastasis in 133 (32.36 per cent).

21. Cunningham, J. H.: Tumors of the Bladder, *J. Urol.* **25**:559 (June) 1931.

Cunningham considered the report on the treatment for benign papilloma by Watson and Cunningham published in 1910. In 287 cases suprapubic operation was carried out by heat, cauterization and snaring and curetting, with an operative mortality of 10 per cent. Recurrence following suprapubic operation took place in 20.4 per cent within three years, and the known recurrences after three years was under 20 per cent. Beer reported 33 cases of benign papilloma treated suprapubically by the latest approved operative technic, with a mortality of 12 and 15 per cent, and a recurrence in eight years. Fulguration of benign tumors through the cystoscope by Beer's method shows the progress made in the treatment of these lesions. In 158 cases reported by Beer there was only one death, the result of bacteremia. Ninety-eight patients were pronounced cured by repeated cystoscopic examinations, and 23 had recurrences. Some of the recurrences did not become apparent until nine years after the destruction of the original growth. In Cunningham's series of 46 cases there was no mortality and eleven recurrences. Nine of the recurrent growths were benign; all of them responded to further cystoscopic treatment.

Twenty years ago, Watson and Cunningham reported an analysis of 279 cases of carcinoma of the bladder. There was an operative mortality by the suprapubic operation, not resection, in 35 per cent, and recurrence within three years in 65 per cent. The treatment included the use of the galvanocautery snare in special instruments, curetting and the application of the cautery in a manner similar to that often used at present, and resection and total extirpation of the bladder. Data obtained with regard to destruction of malignant tumors suprapubically by newer methods, as well as those formerly used, do not differ greatly as to mortality and recurrences. In their series of 38 patients with malignant papilloma and infiltrating carcinoma treated suprapubically by cauterization and diathermy, with or without associated radiation, 6 died in the hospital (15.78 per cent), and 26 died within two years, a total mortality of 83.2 per cent. There has been no marked advance in the treatment of these patients in the last twenty years by the suprapubic method, with the employment of heat. Watson and Cunningham reported a mortality of 35 per cent and recurrence within three years of 65 per cent. Young recently reported a mortality from recurrence of 60 per cent. Cunningham's latest data showed that 83.21 per cent of patients were dead at the end of two years. Cunningham has found that resection offers the best opportunity for cure.

In Watson's and Cunningham's cases of malignant growths there were recurrences in 56.1 per cent. In Beer's cases of malignant papilloma there were recurrences in 25 per cent, and in the infiltrating type in 43 per cent; with both combined the recurrences were in 34 per cent. Young reported recurrences in 59.25 per cent and Cunningham in 69.23 per cent.

Barringer made valuable contributions to the subject of radium emanations implanted into the growths by the suprapubic route and through the cystoscope. Suprapubic operations were done for the implantation of radium in 90 of 94 cases, with 3 deaths (3.18 per cent). In the cases of papillary carcinoma there were 20 patients; 11 (55 per cent) remained free from carcinoma for more than five years. In the 51 cases of infiltrating carcinoma, 12 patients (23.5 per cent) had remained free from the disease for more than five years. Beer employed radium emanations suprapubically by Barringer's method in 31 cases of infiltrating carcinoma. Eleven patients (35.4 per cent) died; these deaths constituted the highest mortality in his experience despite the claim to the contrary.

Diathermy as done at present has rarely proved curative, or accomplished much more than heat applied by the methods in use twenty years ago. Theoretically it is better, and further development may improve its efficiency. At present its value seems to be more as an improved means of destroying growths to be resected, prior to employing radium, and for destroying sloughing, bleeding tumors rather than as a curative measure. The application of roentgen rays as a possible, helpful adjunct prior to operation, as a means of influencing bleeding and as a postoperative procedure, may have some value, but there is no evidence of its success as a curative measure.

It is Cunningham's opinion that cystectomy is an ideal procedure and will long remain a surgical novelty. Uretero-enterostomy and nephrostomy as procedures to deviate the flow of urine from the diseased bladder, but without cystectomy, seem to him to be unnecessary.

Fey and Bompert²² considered the technic of total cystectomy for carcinoma of the bladder. The mortality in approximately 80 published cases was 50 per cent. These cases are isolated, operative technic was varied and usually the lesions were advanced carcinoma for which other treatment had failed. The mortality is much more severe than occurs when the operation is performed in selected cases with regular technic.

The first question considered is the disposition of the ureters. Ureterostomy is a serious operation, but is desirable when infection is present. If the ureters are normal, not dilated or turned out, and have normal peristaltic movements, the results are usually good. If they are dilated, sclerotic or paralyzed, ascending pyelonephritis commonly occurs with fatal result. A two-stage operation, that is, bilateral simple cutaneous ureterostomy and later cystectomy, is preferable. Ureterostomy is performed through bilateral inguinal incisions. Later a transverse

22. Fey, B., and Bompert, Henri: *Technique de la cystectomie totale pour cancer de la vessie*, J. de Chir. **37**:496 (April) 1931.

incision is made several centimeters above the pubic bone. The bladder is freed from the surrounding tissues; the peritoneum is stripped back and opened, and then closed after the manner of Beer and Judd, so as to leave the bladder entirely extraperitoneal. The bladder is then delivered into the incision. By traction on the bladder, the various ligaments and blood vessels are seen, clamped, cut and tied. The prostate gland is usually covered with the bladder, the urethra being cut at the base of the gland. Statistics concerning results are not published.

[ED. NOTE.—Theoretically, total cystectomy would seem to be the ideal treatment for malignant lesions of the bladder. Such tumors tend to metastasize slowly, but their recurrence in situ regardless of the method of removal is common knowledge. As Fey and Bompart emphasize, disposition of the ureters is the greatest obstacle to be overcome in making total cystectomy a practical procedure. It may be hoped that further development of transplantation of the ureters into the intestinal tract, as is now being practiced in a fair number of cases with success, may ultimately make total removal of the bladder and of the prostate gland feasible in dealing with neoplasms of these organs.]

LaRoque²³ described a method of securing complete exposure of the entire bladder in operations for tumor. The patient is placed in the Trendelenburg position and spinal anesthesia is used. The skin, muscle and fascia are divided in a transverse direction. The linea alba is divided to a point an inch or two above the transverse incision through the fascia, and the rectus abdominis and pyramidalis muscles are separated by retractors. No attempt should be made to separate the peritoneum at its point of attachment to the bladder on account of the possibility of tearing the peritoneum. The peritoneal cavity is opened in the transverse direction. With the bladder caught at its top by forceps and pulled upward, another incision is made through the peritoneal covering of the bladder at a point about 5 cm. below its highest attachment. The peritoneum, except at the vertex, can be brushed down so that the entire bladder down to the rectum is free of peritoneal covering, and the ureters and large vessels are brought into view. When this is done, the bladder is held up, and the peritoneal cavity is closed. A gauze sheet is then placed over the line of sutures into the large space made by enucleation of the bladder to protect the line of sutures and cellular tissue against contamination. The bladder is opened at the uppermost portion, and a thorough inspection of the entire interior is made. A wide area of bladder surrounding the tumor in all directions is clamped off, and with an electrosurgical cutting instrument, an area is excised

23. LaRoque, G. P.: Operation for Tumors of the Bladder. *Surg., Gynec. & Obst.* 53:205 (Aug.) 1931.

with a coagulating current, and each edge is touched in other situations. A small, right-angled suprapubic drain is placed in the bladder, and the bladder is closed snugly about it.

MacDonald²⁴ classified growths of the bladder as "probably benign," "certainly malignant" and "doubtful." The treatment for those certainly malignant should be wide resection. The surface is first cauterized, and then actual incision done with the endothermy knife. The ureter is resected and transplanted if the orifice is involved.

Tumors of doubtful classification present the greatest problem of treatment. In 55 cases of this type, 20 proved to be malignant. In the 35 cases which were benign and in which resection was done, the ureter was transplanted in 10 instances without postoperative mortality. In all doubtful cases it is better to subject the patient to unnecessary operation than to palliative operation with diathermy and radium, thereby losing valuable time in cases of malignancy.

Resection was done in 44 cases of the certainly malignant group. The immediate mortality was 13 per cent; 13 deaths resulted from recurrences, 2 from other causes, and 9 patients were not traced, leaving 14 (31 per cent) alive and considered cured if the three year standard is adopted. This limit is considered as too short for an accurate estimation of cures. One of the 14 patients had recurrence seven years after the operation, and another nine years afterward. The lower part of the ureter was resected and transplanted into the bladder in 20 of the 44 cases. This procedure increases the operative risk when there is infection of the bladder, but there was no mortality in benign cases without infection.

Eighty-five (60 per cent) of the definitely malignant tumors were inoperable.

Kidd²⁵ analyzed a series of 32 cases of tumor of the bladder in which diathermy and radon seeds were used. The reasons for selecting the cases were refusal of extensive operation; unsuitable situations of the tumors for partial cystectomy; the possibility that radon would shorten diathermy and make it more secure in cases of pedicled and malignant tumors, and the hope that cystotomy and implantation of radon might prove less difficult and dangerous than partial cystectomy for sessile tumors.

For early favorable cases of pedicled tumors or for small early malignant ulcers, destruction was effected with a diathermy cystoscope. In more advanced cases with a large, broad-pedicled tumor, suprapubic cystotomy was performed. A large bore porcelain caisson is put into

24. MacDonald, S. G.: The Results of Partial Resection of the Bladder for Carcinoma, *Proc. Roy. Soc. Med.* **24**:69 (Nov.) 1930.

25. Kidd, Frank: Treatment of Bladder Tumours by Radon, *Brit. M. J.* **2**:949 (Dec. 6) 1930.

the bladder over the growth, following which a diathermy snare is used and the tumor removed, leaving a charred ulcer. In more extensive cases of malignant sessile tumors the bladder is opened widely, the surface of the tumor is treated with flat button diathermy and the edges of the tumor are surrounded with a ring of threaded radon seeds at appropriate intervals.

Kidd divided his results into three groups: In the first group are 13 cases of malignant tumor with thick pedicles, bald and without fimbria. Eight patients were treated cystoscopically; 2 aged more than 80 years died, and 5 were living and well without recurrence from two to seven years after treatment. Five patients were treated with cystotomy and the diathermy snare with implantation of radon; all were living and well from two to five years afterward. Radon was apparently most successful in this group. Although the diathermy may have been sufficient to cure, the use of radon seeds gave additional security against recurrence. In the second group are 14 cases of small, early, malignant sessile tumor, without pedicles, some papillary and some ulcerous, but all infiltrating. Four patients were treated by diathermy and radon cystoscopically; 3 are living and well from four months to seven and a half years after treatment. One patient died within four months of pyelitis and uremia. Nine patients were treated by cystotomy, diathermy and radon implantation; 6 died. Of the 14 patients treated, 6 survived operation. Eight died, 2 as a direct result of the treatment, 4 from rapid internal recurrence apparently induced by radon, and 2 from late internal recurrence. In only 6 of the 14 cases was the use of radon successful. It is in this diffuse type of growth that radon is not so likely to influence the growth. In the third group were 5 cases of malignant sessile tumor. Four patients died and 1 patient is alive, but recurrence is likely to develop.

Kidd stated that the hypothetic advantages for the use of radon in the bladder are that it may produce local destruction of neoplastic tissue with less mutilation than is possible by resection; it may produce fibrosis and shrinkage around the edge of the growth; it may produce obliterating endarteritis in the vessels supplying the growth, and thus stop bleeding and cause death of the center of the growth; it may sometimes render an inoperable growth operable, or it may occasionally produce unusual cure.

The disadvantages and dangers of radon are that it produces only local destruction of growth and cannot destroy distant extensions and metastatic growths; it is likely to produce painful burns, sepsis, sloughing, septicemia and pulmonary complications; it has a definite operative mortality which is as high as that of any other method, even of resection. and it may even stimulate a growth.

White²⁶ reported a case of fibromyoma of the bladder of a child aged 7 years. The tumor was successfully removed surgically.

Malignant tumors of the bladder of infants usually do not run a course of more than five months, whereas benign tumors, including fibromyomas, may run a considerably longer course. The significance of benign tumors of the bladder is in their situation: If high and on the posterior wall, they may not cause marked symptoms, or if they are in the region of the neck or trigone, especially if furnished with a long pedicle, they may interfere with urination by plugging the vesical orifice. The treatment for these benign tumors is essentially surgical, and the prognosis, both as regards recurrence and life, is favorable provided excision is thorough and the base of the tumor is fulgurated.

Kretschmer²⁷ stated that mesothelial tumors, both benign and malignant, are rare and form a small percentage of tumors of the bladder. He reported in detail the case of a girl, aged 19, in which resection of the bladder was performed successfully for leiomyoma.

Forty-seven authenticated cases of vesical myoma, excluding Kretschmer's case, are reported in the literature. It is generally stated that 90 per cent of all neoplasms of the bladder are epithelial in origin, and the remaining 10 per cent are mesothelial or embryonic. One patient was aged less than 20 years; 7 were between 20 and 30, 8 were between 30 and 40, 9 were between 40 and 50, 11 were between 50 and 60, and 5 were more than 60; in 6 cases the age was not stated. The tumors occur with about equal frequency among both sexes.

Myomas of the bladder may not cause symptoms, as revealed by the fact that in a number of cases the lesion was found incidentally at necropsy. If the tumor is intramural or subserous, its development progresses until symptoms of pressure resembling those of any abdominal or pelvic growth are noted. In a number of cases there was a palpable abdominal tumor. When the tumor is submucous, vesical symptoms occur. In case the tumor encroaches on the ureteral orifice, symptoms of obstruction may result before it becomes large. Complete retention developed in several cases.

Surgical treatment was carried out in 40 cases. In Saturski's case the pedicle of a submucous tumor was sectioned by cautery, and almost immediately pains resembling labor pains occurred, and the tumor was expelled through the dilated urethra. In 7 cases in which surgical treatment was not carried out, the tumor was discovered at necropsy.

26. White, E. W.: A Very Rare Bladder Tumor (Fibromyoma) in a Child, *J. Urol.* **26**:253 (Aug.) 1931.

27. Kretschmer, H. L.: Leiomyoma of the Bladder with Report of a Case and a Review of the Literature, *J. Urol.* **26**:575 (Oct.) 1931.

Stone.—Noble²⁸ compared the results of the analysis of 200 cases of vesical calculi at Siriraj Hospital, Bangkok, during the last three years with those of India and China and with the disease as seen in Europe at the present time and one hundred years ago. Of the 200 patients, 196 were males and 4 were females; almost 50 per cent of the patients were aged between 20 and 50 years. In Siam, stone in the bladder occurs most frequently in the first decade of life, and its frequency diminishes toward adult life and old age. In the Orient, it is a disease of childhood and adolescence; in Europe, it is a disease of late middle and advanced life. The statistics of Civale in France and Yelloly in England of a hundred years ago show that stone in the bladder at that time was a disease of childhood; with improved conditions of laborers in those countries, stone in the bladder among children has gradually disappeared.

Chemical analysis is necessary in most cases to determine the true composition of vesical calculi. Newcombe and Ranganathan examined 221 vesical stones collected from the various provinces in India and gave as the approximate composition of the average vesical calculus the following: calcium oxalate, 24.9 per cent; calcium phosphate, 7.4 per cent; magnesium ammonium phosphate, 6.9 per cent; protein, 6.2 per cent; uric acid, 49.7 per cent, and other substances, 4.9 per cent. Thompson's figures from Canton hospital are uric acid and urates, 71 per cent; phosphates, 16 per cent, and oxalate, 8 per cent. In 1842, Bence-Jones gave the following analysis from England of 1,000 stones: uric acid and urates, 60.5 per cent; phosphates, 23.3 per cent, and oxalate, 14.2 per cent. In England and America at the present time most stones in the bladder are crushed, so that it is difficult to obtain percentages. Cabot has stated that the oxalate stone is the most common type in the infected bladder. Nakano, a Japanese worker, according to Swift Joly, stated that the following composition is fairly indicative of vesical stones found in England today: uric acid and urates, 23.3 per cent; phosphates, 19.4 per cent; oxalate, 32.3 per cent; mixed, 16 per cent; cystine, 1.4 per cent, and foreign body, 5.3 per cent.

In the Far East, stone in the kidney is rare compared with stone in the bladder. Newcombe and Ranganathan noted only 5 renal calculi in 226 cases analyzed. In China, Thomson found there were 512 vesical to 4 renal stones. In the Siriraj Hospital, there were only 7 cases of renal stone as compared with 200 cases of vesical stone occurring in the three year period. In St. Peter's Hospital in London, one fourth of all stones in the urinary tract are in the kidney.

The relationship of vitamin A to the formation of stone in the bladder in children is probably indirect. Children are more likely to suffer from a diet deficient in vitamin A than adults. In Siam, the

28. Noble, T. P.: Vesical Calculus in Siam, *Brit. J. Urol.* 3:14 (March) 1931.

children who have vesical stones had had a diet defective in vitamin A. This vitamin may affect the formation of stones by removing the protective colloids from the urine. Certain colloids in the urine have a protective action and prevent the precipitation of salts. The total amount of colloid in the urine appears to be dependent on the diet, and is increased on a diet rich in protein. It is possible that the action of vitamin A removes the protective action of the colloids, and the salts are precipitated.

[ED. NOTE.—Vesical calculus is the type which is known to be prevalent in certain parts of the world as endemic. Dalmatia, the Indian Punjab, the Canton province of China, and Rumania are examples of stone centers. Osborne, Mendel and Perry, in 1917, first demonstrated that deficiency of vitamin A in the diet would produce calculi in the bladder of rats. The theory of dietary deficiency has been advanced by Ratschitch, Joly, McCarrison and others to account for the vesical calculi of children who live in localities where such stones are prevalent. Hager and Magath isolated *Salmonella* and *Proteus ammoniae*, urea-splitting organisms, from the urine of patients with cystitis and alkaline encrusted bladders and with urinary calculi. Although more is known of the cause of vesical calculi, just how the various factors of vitamin deficiency and infection bring about changes in the urinary colloids and cause a calculous type of crystalline precipitation is yet to be determined.]

Kearns and Turkeltaub²⁹ stated that beneficial effects may possibly be obtained by the addition of vitamins to the usual methods of treating calculous disease. No harmful effects result, and there is often marked improvement in the general health of the patient. Formerly, elimination of foci of infection, often by radical measures, was stressed. In spite of eradication of these foci of infection in many cases, symptoms of the same prostatitis or pyelonephritis still remained. The authors reported a case in which removal of infected teeth and tonsils, with treatment by vitamins, resulted in cure of a severely encrusted bladder with cystitis.

Diverticulum.—Fowler³⁰ reported a case of vesical diverticulum treated in an unusual way. The bladder was opened widely over the vertex. The orifice of the diverticulum was located on the base of the bladder behind the trigone to the left of the median line incision. It admitted the index finger and was surrounded by a dense, unyielding ring of fibrous tissue. The bladder was otherwise normal. A pair of Allis clamps was introduced into the diverticulum, and the wall was grasped and brought up through the opening into the cavity of the

29. Kearns, W. M., and Turkeltaub, S. M.: Encrusted Cystitis, *J. Urol.* **26**: 465 (Sept.) 1931.

30. Fowler, H. A.: Vesical Diverticulum, Complicating Prostatic Obstruction: Report of an Unusual Case, *J. Urol.* **26**:261 (Aug.) 1931.

bladder. By repeating this maneuver more than half of the diverticulum was delivered into the bladder. Further invagination was then impossible on account of adhesions at the base of the sac to the structures beneath. An incision was then made through the mucosa of the bladder, completely encircling the orifice, about 1 cm. from its margin. The mucosa was dissected toward the orifice, was grasped with clamps, forming a cuff of mucous membrane continuous with the lining of the diverticular sac. By traction on this cuff with the left hand, the freely movable portion of the sac was drawn up into the orifice and its mucosal lining was separated by gauze dissection and drawn into the bladder. After enlarging the opening of the diverticulum, a narrow blade retractor was inserted, and by retraction the index finger covered with gauze could be introduced at one point and further separation of the lining continued within the sac. By changing the position of the retractor, this process was continued around the circumference of the sac. The opening between the diverticulum and the bladder was closed, and the diverticulum drained extravesically. Later the prostate gland was removed. A good functional result was obtained.

Peacock and Corbett³¹ stated that primary carcinoma in diverticulum of the bladder is more common than is indicated by the number of cases reported. Thorough examination of diverticula often reveals the presence of carcinoma. The diagnosis is extremely difficult. Hematuria with a diverticulum as the origin, as well as imperfect filling defects as revealed in diverticulograms, is suggestive of carcinoma. Diverticula occurring with prostatic hypertrophy should be removed if they are large and thoroughly exposed

Exstrophy.—Cabot³² stated that earlier attempts at plastic operation for the cure of exstrophy of the bladder were not successful, partly because of inherent difficulties or unsatisfactory closure and partly because of the impossibility of creating a satisfactory sphincter. Transplantation of the ureters to the large intestine, beginning with the method of Maydl, was only partially satisfactory because of rather high immediate mortality and resulting injury to the kidneys from obstruction to the outlet of the ureters, with dilatation and progressive deterioration of the upper part of the urinary tract. The problem of treating exstrophy by ureteral transplantation differs from the general problem of ureteral transplantation in that the patients are children, the ureters and kidneys are generally normal, and time is not an important factor.

31. Peacock, A. H., and Corbett, D. G.: Primary Carcinoma in Diverticula of the Urinary Bladder, *J. Urol.* **25**:625 (June) 1931.

32. Cabot, Hugh: The Treatment of Exstrophy of the Bladder by Ureteral Transplantation, *Proc. Staff Meet., Mayo Clin.* **6**:422 (July 15) 1931.

Fourteen cases are reported in which a two-stage ureteral transplantation, chiefly extraperitoneal, was carried out. These operations were done over a period of ten years, and the average age of the patients was 8 years. There was no mortality, either immediate or remote. The patients are well at a period varying from one to ten years after operation. Two women passed through three normal labors.

Coffey's principle of ureteral transplantation to the large intestine has been more satisfactory than any method previously employed. In cases of exstrophy of the bladder or epispadias in which other operations have failed, the three-stage method of operation gives a low mortality and satisfactory results. There is some evidence to support the view that this method gives better late results than previous methods of transplantation.

Submucous Fibrosis.—Smith³³ stated that there is apparently sufficient evidence that submucous fibrosis is due to an infected focus to warrant careful exclusion of such foci. The condition is usually accompanied by a urethral lesion which requires treatment. Electrocoagulation through the cystoscope and supplemented by urethral treatment is the most satisfactory method of treatment in these cases. The author reported 5 cases of submucous fibrosis treated by electrocoagulation, together with regular dilation of the bladder and urethra, in all of which marked improvement resulted.

Incontinence.—Johnston³⁴ described his operation of apposing the torn ends of the sphincter muscles of the urethra in most cases of urinary incontinence following childbirth. The method was successful in 5 of 6 cases. The lithotomy position is used, and a Pezzer catheter is introduced into the bladder. Gentle traction on the catheter reveals the neck of the bladder. The anterior vaginal wall is incised mesially from a little above the urethrovesical juncture down toward the meatus, and the vaginal flaps are reflected laterally. The thickened neck of the bladder can then be felt. Directly below and stretching from side to side can be seen the deep layer of the trigone. By careful dissection far out on the sides just below this layer, the torn ends of the sphincter can be isolated. These ends are usually far out and pulled upward and outward. The sphincter muscle of the urethra has no sheath; the sheath of this muscle and that of the deep transversus perinei differentiate to form the two layers of the trigone, so that in the majority of these cases the deep layer is relaxed or partially torn. Advantage is taken of this condition to include the deep layer of the

33. Smith, G. G.: Experiences with Submucous Fibrosis of the Bladder, *J. Urol.* 26:455 (Sept.) 1931.

34. Johnston, H. W.: Urinary Incontinence Following Childbirth: Its Surgical Treatment, *Surg., Gynec. & Obst.* 53:97 (July) 1931.

trigone in the first stitch. This tough membrane aids in holding the ends of the muscle in place, and prevents the tearing out of stitches before healing is complete. The redundant vaginal mucosa is then excised, which obliterates the dead space, helps to support the urethra and tends toward healing.

Obstruction.—Hepburn³⁵ stated that detachment of the trigone muscle is a congenital condition and may be precipitated, like hernia, by unusual strain such as obstruction to the outlet of the bladder. Contraction of Bell's muscles in the detached trigone will cause the base of the trigone, or interureteric muscle, to slide up toward the outlet of the bladder. This action deprives Bell's muscles of their function of pulling open the internal sphincter. The trigone muscle becomes an obstructing valve-like dam. This condition may be confused with compensatory hypertrophy of the trigone. The treatment is surgical, and the operation of making a trough through the obstructing trigone, as described by Young, gives good results.

PROSTATE GLAND

Hypertrophy.—Boit³⁶ analyzed 114 unselected cases of adenoma of the prostate gland in which roentgenotherapy was used. Eight cases were described as first-stage hypertrophy, 22 as second stage, 78 as third stage, and 6 as acute retention. On three successive days three fields of 6 by 8 cm. were irradiated over the anterior and posterior pelvis and over the perineum. The dose for each area amounted to 80 per cent erythema dose, which led to a dose of about 94 per cent effective in the prostate gland. The testes were protected. Shortly before each treatment the bladder was emptied, washed with a solution of boric acid, an enema was given and 10 cc. of 50 per cent dextrose solution was injected intravenously. If necessary, the treatment was repeated at intervals of four weeks.

Ten of the 114 patients died from other diseases during the treatment. Ninety-one patients were free from symptoms and had no retention; this number included the 8 patients with first-stage hypertrophy and the 6 with acute retention. Six patients were improved, having a retention of from 10 to 200 cc. Seven patients did not improve. Carcinoma was found in one case at necropsy. Fifty-one patients were traced by letter, and 35 were examined from one to five years after treatment. Twenty-eight of the 51 traced patients had died, 11 from other diseases, 12 from complications of the prostatic disease and 5

35. Hepburn, T. N.: Mobility of Trigone a Cause of Bladder Obstruction, *J. Urol.* **26**:591 (Oct.) 1931.

36. Boit, H.: Erfahrungen mit der Röntgenbestrahlung bei der Prostatahypertrophie, *Deutsche med. Wchnschr.* **57**:351 (Feb. 27) 1931.

from unknown causes. Twenty-three were alive at the time of inquiry; the function of the bladder of 15 was good; of 5 satisfactory, and of 3 poor. Of the 35 patients examined, 19 had no retention and 16 had retention from 10 to 95 cc. In more than 50 per cent of all cases the result was good from one to five years after treatment; in about 25 per cent it was satisfactory, and in the remaining 25 per cent it was poor. In 30 per cent of the cases there was recurrence; about a third of these patients responded to additional treatment.

Treatment must not be repeated too often as it may lead to fibrosis of the *pars prostatica*, causing the same symptoms as stricture. Thirty-two patients remained well longer than one year; 13 were well for one or two years, 9 for two or three years, 8 for three or four years and 2 for four or five years.

Boit concluded that roentgenotherapy, with relatively high doses, is the method of choice in inoperable cases of adenoma of the prostate gland. In the operable cases of the second and third stages, prostatectomy is preferable. If operation is not done, irradiation usually offers good results, which may be improved by further development of the technic of treatment.

Bacon, Kretschmer and Woodruff³⁷ analyzed 321 unselected cases of prostatic obstruction to determine the frequency and predominant types of associated heart disease. Chronic myocardial degeneration, accompanied usually by arteriosclerosis, was noted in 115 cases, in 90 (78 per cent) of which electrocardiograms were abnormal. In the 277 cases (70 per cent) the patients between the ages of 60 and 80 years (39.2 per cent) showed definite evidence of myocardial disease. There was greater frequency of higher systolic blood pressure in the presence of myocardial changes than in the corresponding cases in the apparent absence of heart disease. In cases of decompensation, long periods of rest in bed were required with maintenance doses of digitalis. Slow decompression of the bladder in acute retention is particularly important in these cases. The most favorable results were obtained with sacral anesthesia. It does not produce the marked fall in blood pressure that accompanies spinal anesthesia, nor does it produce the cardiac embarrassment or respiratory complications associated with ether, ethylene or nitrous oxide.

There were 4 postoperative deaths directly attributed to heart disease. Two of the patients had coronary thrombosis; 1 had manifested definite evidence of severe myocardial injury, although death did not occur until after repair of the suprapubic fistula, thirty-seven days after

37. Bacon, C. M.; Kretschmer, H. L., and Woodruff, L. W.: Prostatic Obstruction: Electrocardiographic Study of 321 Cases; A Further Report, *J. A. M. A.* 97:1221 (Oct. 24) 1931.

prostatectomy. Forty-seven patients who were examined a considerable time after operation showed general improvement in cardiac function as a result of the relief obtained from operation.

Electrocardiograms emphasize the value of recognizing preoperatively the presence of cardiac disease in cases of prostatic obstruction irrespective of clinical cardiac signs. The electrocardiogram must be considered only an aid, not the final criterion, in the diagnosis of myocardial disease.

Herbst³⁸ considered pulmonary embolism, its causes and their elimination and control to reduce the mortality from this surgical accident. The slowing of the blood stream with stasis has been combated by early movement of the patient's limbs and body following operation. A consideration of the etiology of this condition should include not only the cases of the larger emboli causing sudden death, but the complications produced by small emboli that do not result in immediate death but seriously disturb convalescence and may be a factor in the fatal outcome from other causes. The clinical picture of the larger embolus that lodges in the lung and causes death instantly or within a few hours is characteristic and diagnosis is not difficult. The cases in which the arrival of the embolus in the lung is followed by severe localized pain, disturbances of respiration and the expectoration of bloody mucus or pure blood is also easily identified. In another group of cases the symptoms are not so characteristic and may be overlooked or diagnosed as bronchopneumonia, pleurisy or bronchitis. The condition may be present for weeks in these cases, and complications such as abscess of the lung and empyema may develop.

It is Herbst's opinion that infection contributes to the development of pelvic thrombosis which is the common forerunner of pulmonary emboli. These emboli rarely come from thrombosis of veins of the lower limbs.

In regard to infections by catheter prior to prostatectomy, Keyes stated that preparation for prostatectomy is done by catheter when it seems feasible, and that preliminary suprapubic drainage is reserved for the chronically overdistended and infected bladder and when the use of the catheter causes unfavorable symptoms. To exclude from published statistics the deaths that occur before prostatectomy is performed is misleading as to the frequency, gravity and preventibility of infection by catheter. Herbst believes that some of the infection complicating the treatment of prostatic obstruction occurs during the period of preparation. The reduction in mortality following the introduction of preoperative study and two-stage prostatectomy led to bolder procedures being carried out. Drainage by catheter followed by a one-

38. Herbst, R. H.: President's Address, *J. Urol.* 26:167 (Aug.) 1931.

stage prostatectomy with visual removal of the prostate gland was adopted in many cases. Adenoma of the prostate gland is usually associated with infection in the gland itself, the urethra, the seminal vesicles or the upper part of the urinary tract. Such infection is almost certain to be stirred up by the presence of the indwelling catheter, and even in cases in which there is no infection at the start, infection may occur from the treatment.

Neff³⁹ stated that exposure of the bladder preliminary to cystostomy and other operations has invariably prevented any serious infection of or about the suprapubic wound. The method has great value for the patient who is a poor risk, and the patient with a severely infected prostate gland, the patient with a fat abdominal wall and for all patients who require lithotomy for stone. Open operation on the prostate gland and bladder can be easily done, and with the same relative gain in healing of the wound that is observed for simpler operations. Temporary looped sutures can be placed at the time of exposure for the purpose of guiding permanent sutures into position later, thereby gaining the same protective reaction for suture tracks as for the main wound.

Recurrence.—Cochems⁴⁰ found 17 reported cases of recurrence of enlargement of the prostate gland with histologic evidence that the recurrence was benign. Recurrent glandular hyperplasia of the prostate gland results from growth of tissues remaining after total prostatectomy, by which usually only the hyperplastic periurethral glands are removed. Although the usual hyperplasia of the prostate gland arises in the inner glands, it has been shown that occasionally it occurs in the outer glands. Following enucleation of the inner glands, there may be hyperplasia in the outer glands, or surgical capsule, which then becomes a true recurrence.

Cochems reported a case of recurrence of the prostate gland fourteen years after total suprapubic prostatectomy. Necropsy was performed. The recurrent small left lobe seemed to have had its origin from a fragment of tissue from the inner gland, remaining attached to the inside of the prostatic capsule, whereas the large recurrent right lobe apparently arose from the compressed true prostatic tissue within the capsule. The histologic structure was not unlike the usual glandular hyperplasia of the prostate gland.

Cunningham⁴¹ reported 3 cases of recurrent prostatic obstruction, and stated that reports reveal about 1 per cent return of this condition.

39. Neff, J. H.: Exposure of Bladder as Step Preliminary to Cystostomy, Prostatectomy, and Lithotomy, *Am. J. Surg.* **13**:40 (July) 1931.

40. Cochems, F. M.: The Recurrence of Benign Enlargement of the Prostate, *J. Urol.* **25**:661 (June) 1931.

41. Cunningham, J. H.: Recurrent Benign Prostatic Obstruction, *J. Urol.* **26**: 271 (Aug.) 1931.

Several hypotheses are propounded as to the cause of recurrence of benign prostatic hypertrophy. Takahaski suggested that the prostatic capsule is a tissue composed of flattened glands which will take on activity of regeneration of the gland when the pressure has been removed by the prostatectomy. Fraudenberg is of the belief that the regeneration takes place from small, adenomatous nodules left at the time of the first prostatectomy.

Jacoby divided the glands of the prostatic urethra into mucous, submucous and prostatic. The submucous glands form the cervical group about the vesical neck and may give rise to the pathologic middle lobe; they are also situated on the anterior or ventral wall of the urethra. By histologic study he claims to have demonstrated that these two groups can develop even into the muscularis. Furthermore, the urethral glands are not the only ones to undergo hypertrophy; on each side of the ventral group there is a particular glandular zone, often continuous with the prostatic glands, which is the site of the hypertrophic centers. As they are continuous with the prostatic glands in the prostatic capsule, nuclei of hypertrophy may exist. These so-called nuclei of hypertrophy normally play only a secondary part, but become active after extirpation of the central glandular tumor which has compressed them, and may undergo such expansion as to form new prostatic tissue, even to the point of producing obstruction by overgrowth.

Leiomyoma.—Hinman and Sullivan⁴² reported 2 cases of benign leiomyoma presumably of the prostate gland, producing rectal symptoms and mild prostatism. The round leiomyomatous tumor in the first case was encapsulated and extraprostatic, being attached to the prostatic capsule by a short fibrous pedicle. The tumor in the second case was entirely contained within the prostatic capsule and apparently was primary in the posterior lobe. Leiomyoma of the prostate gland is rare; only 4 cases were noted in current pathologic literature.

Stone.—Eisenstaedt and McDougall⁴³ reported a case of prostatic stone which, by increase in size, produced pseudodiverticulum of the urethra. They stated that calculi of this type have been described as urethral diverticular stones. True stones in the prostate gland are always multiple and have as a nucleus organic material, the corpora amy-lacea. The etiology of prostatic calculi is not definitely known but they are often associated with other genito-urinary lesions. Diagnosis of the condition is aided considerably by the roentgenogram. Treatment by perineal prostatotomy is preferred even when the stone communicates with the urethra.

42. Hinman, Frank, and Sullivan, J. J.: Two Cases of Leiomyoma of the Prostate, *J. Urol.* **26**:475 (Sept.) 1931.

43. Eisenstaedt, J. S., and McDougall, T. G.: Prostatic Stone Causing Pseudodiverticulum of the Posterior Urethra, *J. Urol.* **25**:639 (June) 1931.

PENIS

Carcinoma.—Maxwell and Moran⁴⁴ reported a case in which mild chronic balanitis, with tight, redundant prepuce, developed into granulomatous thickening of the prepuce and an indurated cauliflower-like tumor about 1 cm. in diameter. The diagnosis of squamous cell carcinoma was confirmed by biopsy. The glands in the groin were palpable but were thought to be normal or mildly inflammatory.

A mold of Colombia paste 1.5 cm. thick was made to cover the entire length of the penis. Thirty-five milligrams of radium element in seven foci were disposed around the circumference of the mold, with a filtration of 0.5 mm. of platinum. The testes were protected with lead sheeting. A minimal time of exposure of four days is desirable; in the present case, applications were made for ten hours daily over a period of eighteen days. The radium reaction disappeared at the end of six weeks, and the epithelium at the end of three weeks. The glands of the groin were not treated, and after fifteen months there was no sign of metastasis. If there is any suspicion of glandular masses, surgical excision should be done, followed by deep irradiation or by the application of radium at a distance.

Young⁴⁵ reported his technic for cure of carcinoma of the penis, which he has recently made more radical but still conserved the root of the penis and the sexual powers. The procedure consisted of extensive block dissection of the fat surrounding the glands of the groin, the pubic region, the upper portion of the thigh and fatty prolongations into the upper portion of the scrotum. Included in the dissection were the lymphatic and surrounding structures along the base and root of the penis in continuity with the portion of the penis amputated for removal of the growth. The recent modification to make the procedure more radical includes removal of Buck's fascia, which surrounds the corpora cavernosa and urethra, to the root of the penis, and insures complete removal of the dorsal lymphatic structures.

As now performed, the operation is as follows: The region of the tumor is covered with tightly fitting, antiseptic dressing. Care is taken thoroughly to sterilize the operative field, as the carcinomatous lesion is usually markedly infected and probably responsible for frequent post-operative suppuration. A semilunar incision is made from a point near the anterior superior spine of the ileum on one side to the other. The lower part of this incision is just above the base of the penis, and through skin and fat. From the most dependent portion of the incision

44. Maxwell, W., and Moran, H. M.: Epithelioma of the Penis Treated by Radium, *M. J. Australia* 1:409 (April 4) 1931.

45. Young, H. H.: A Radical Operation for the Cure of Cancer of the Penis, *J. Urol.* 26:285 (Aug.) 1931.

two parallel longitudinal incisions are made about 2 cm. apart, one on each side of the shaft of the penis down to the point at which amputation is to be carried out. A circular incision is then made around the inferior surface of the penis from one of these longitudinal incisions to the other, but the skin across the dorsum is not divided by the circular incision. The incisions along and around the penis are only superficial, and do not extend to Buck's fascia, which encircles the corpora cavernosa. The skin is elevated at the upper angle of the wound in the groin, subcutaneous fat and glands are dissected cleanly from the deep fascia, proceeding from above downward. As this fatty glandular mass is carried downward, the anterior surface of the inguinal canal, the external rings and the spermatic cords with their fascial coverings are exposed. When the scrotum is reached, the fat which accompanies the spermatic cord is followed for a short distance down the scrotal sac, so as to secure any lymphatic vessels or glands which might lie in the upper part of the scrotum. The skin surrounding the base of the penis is then dissected backward for a short distance, exposing Buck's fascia, which covers the corpus cavernosum and spongiosum. A longitudinal incision is then made through Buck's fascia along the undersurface of the corpus spongiosum, and Buck's fascia is then dissected up from the right lateral aspect of the spongiosum and cavernosum until the suspensory ligament is reached, when this fascia is divided transversely. The corpus spongiosum is then divided obliquely, and the corpora cavernosa transversely at a point from 1.5 to 2 cm. farther back. The ends of the corpora cavernosa, which had been clamped to avoid hemorrhage, are brought together. The urethra, which projects from 1.5 to 2 cm. beyond the stump of the ligated corpora cavernosa, is then sutured into the skin, which is drawn over it along the dorsum by interrupted sutures.

[ED. NOTE.—A fair opportunity for cure of carcinoma of the penis is offered by surgical treatment according to Young's technic. Advocates of radium therapy, such as Ferry, Monod, and Maxwell and Moran, are increasing. There is some evidence to show the superiority of radium if properly applied before the growth has penetrated Buck's fascia or metastasized to the inguinal or possibly to the deep pelvic nodes.]

It is generally conceded that phimosis is at least an aggravating cause, and that circumcision in early life will tend to prevent the occurrence of this distressing lesion. Probably the operation of Young represents the best therapeutic method of attack at the present time.]

Lewis ⁴⁶ reported 34 cases of radical operation for carcinoma of the penis done by Young's method. Thirty-one patients left the hospital

46. Lewis, L. G.: Young's Radical Operation for the Cure of Cancer of the Penis: A Report of Thirty-Four Cases, *J. Urol.* **26**:295 (Aug.) 1931.

with their wounds healed and were voiding freely through the newly formed meatus in the penile stump. Fifteen of these patients are living, 8 have not been located and 8 have died. One patient has lived sixteen years since operation without recurrence of tumor.

Patients who came for operation within one year after noting the initial lesion and without metastatic involvement of the glands are the best risks. There were 10 in this group, 8 of whom are well and 2 have not been located. Sixteen patients came for examination within two years after noting the initial lesion; 11 are living and well, 3 have not been located and 2 have died. Of 5 patients who were not examined until after five years' illness, 2 are living and well, nine and eight years, respectively. One patient was well three years after operation and cannot be located. One patient has not been traced and 1 died of metastasis to the lungs three years after operation. Of the 15 patients without metastatic involvement, the average life since operation is four and eight-tenths years. Eight patients with metastasis lived an average of two and a half years after operation.

In this series of cases there was no instance of recurrence in the penile stump, none of postoperative extension to the scrotum or contents and no appearance of recurrence in the operative field (genitalia or groin) when complete radical resection was done.

The high incidence of phimosis before evidence of malignancy of the penis appears was noted by Dean to be 74 per cent in 75 cases. Barney reported 85 per cent in 100 cases. Wolbarst, in commenting on circumcision as a prophylactic, concluded that circumcision done in infancy is a decisive factor in the rarity or absence of carcinoma of the penis in Jews.

TESTIS

Undescended Testis.—Cabot and Nesbit⁴⁷ called attention to the variance of opinion as to the incidence of undescended testis. Zeibert, in 1898, reported an incidence of 0.2 per cent in 6,962,543 examinations in the Austrian army between 1870 and 1882. Beven estimated the incidence as 1 in 500. The War Department of the United States reported 3.1 to 1,000 men examined for the draft.

Cryptorchidism occurs most frequently on the right side. There is no constant etiologic factor in this deformity, although the shortness of the spermatic vessels presents the greatest difficulty in placing the testis in the bottom of the scrotum. The undescended testis is generally found to be somewhat smaller and of softer consistence than the normal testis. Associated indirect inguinal hernia of some degree is the rule, although this is not true in all cases.

47. Cabot, Hugh, and Nesbit, R. M.: Undescended Testis: Principles and Methods of Treatment, Arch. Surg. 22:850 (May) 1931.

Cabot and Nesbit described a method of orchiopexy that utilizes the principle of constant traction. An incision is made in the skin extending from the internal inguinal ring down to the neck of the scrotum. The inguinal canal is opened, and the external ring is incised. The testis and cord are then exposed and isolated. The processus vaginalis is next dissected carefully from the cord and dealt with as any indirect inguinal hernial sac. When a complete hernial sac is found, the lower end of the processus vaginalis is not closed, as hydrocele is almost certain to result. The cord structures are then freed. With one finger in the retroperitoneal space, the spermatic vessels are freed from the posterior surface of the peritoneum. The cord will then permit a fairly normal descent of the testis. A finger is next pushed down into the scrotum to establish a bed in which the testis is to lie. A suture is passed through the remains of the gubernaculum and tied so that the two ends can be used for traction on the testis. The needles are then introduced and pushed out through the skin at the lowest point. With the sutures so placed, the testis is drawn down into the scrotum. The sutures are then attached to a wire frame and rubber band so as to produce constant gentle downward traction on the testis. The traction thus applied is left on for about twelve days, being adjusted occasionally during that time so as to remain constant.

In a series of 25 cases covering a period of two years, bilateral undescended testes occurred in 6; 13 occurred on the left side and 6 on the right. Recent data concerning 17 cases revealed that the testis was in the normal position in the scrotum in 10, and in the upper part of the scrotum in 7; in none was it at a higher level. In 13 cases the testes were of normal size; 2 were slightly larger than normal, 1 was slightly smaller than normal, and 1 was definitely atrophic.

Metcalf⁴⁸ reported a case of tubular hermaphroditism. The man was aged 31 years, married, well developed and apparently normal except for the presence of an abdominal tumor, undescended testes and a right indirect inguinal hernia.

Laparotomy disclosed a rudimentary uterus 18 cm. long, and two fallopian tubes. There was a testis at the fimbriated extremity of the left side and on the right side a large embryonal carcinoma or teratoma of the testis. There was a normal appearing vas deferens lying in the angles between the uterus and fallopian tubes.

This is a perfect example of tubular hermaphroditism in which there is complete development of the mullerian and wolffian ducts. This condition must be distinguished from true hermaphroditism or glandular

48. Metcalf, R. H.: *Uterus Masculinus: Complete Tubular Hermaphroditism, with Teratomatous Enlargement of an Undescended Testicle*, Brit. J. Surg. **18**: 335 (Oct.) 1930.

hermaphroditism in which both ovaries and testes exist in the same person. The arrangement of the feminine organs in this instance was more perfect than in any case previously reported. Primrose, in 1898, reported a similar condition with associated teratoma of the undescended testis.

Klages⁴⁹ reported a case of testicular carcinoma associated with tuberculosis of the epididymis. The epididymis had been excised for tuberculosis two years before. One year before, the patient was again suffering from pain in the right testicular region, and, as the testis was enlarged, the growth was excised and found to be carcinoma.

The growth appeared to arise on the epithelium of the seminal tubules. Sarcoma-like tissue was also present in various areas, and numerous infiltrating lymphocytes. Necrosis was extensive. Tissue from the right inguinal region showed tuberculosis in some lymph nodes and areas of the tumor cells in others. The material from the left inguinal region showed metastatic tumor. Klages believed that the tuberculosis of the epididymis acted probably as a chronic irritant on the testicular tissue.

[ED. NOTE.—Tuberculosis and malignant neoplasms are rarely found simultaneously, although from time to time such reports occur in the literature. Klages' case is of interest, especially since he found tuberculosis and carcinoma cells as metastatic lesions in the regional lymph nodes.]

NEUROSURGERY

Learmonth⁵⁰ stated that operations on the nerves of the bladder must be based on accurate knowledge of functional anatomy if they are to be used in the treatment of vesical diseases. With the exception of the inconsiderable filaments which join the hypogastric ganglions direct from the sacral paravertebral sympathetic chains, the majority of the sympathetic nerves of the bladder reach it by way of the presacral nerve. For the surgical exposure of the sympathetic nerves of the bladder, Learmonth has used the left paramesial incision, a third of the incision being above the umbilicus, and two thirds of it below. The packing off of the intestine, to expose the posterior abdominal wall, is much facilitated by the use of spinal anesthesia. The peritoneum over the promontory is picked up, and incised in a vertical direction, to the upper limit of the exposure. Each lip of the peritoneal incision is then carefully retracted. A strand may be identified as it passes over the left

49. Klages, Friedrich: Hodenkrebs bei alter Nebenhodentuberkulose, *Ztschr. f. Krebsforsch.* **31**:587, 1930; abstr., *Am. J. Cancer* **15**:506 (Jan.) 1931.

50. Learmonth, J. R.: Neurosurgery in the Treatment of Diseases of the Urinary Bladder: I. Anatomic and Surgical Considerations, *J. Urol.* **25**:531 (June) 1931.

common iliac vein. This strand is then placed on a blunt hook, and as further strands are identified, first toward the median line and then toward the right common iliac artery, they are in turn placed on the hook. At the conclusion of the dissection the common iliac arteries and the left common iliac vein should be denuded of nerve fibers. The nerve is now divided between ligatures, as high as possible. The peripheral end is raised by blunt dissection with a cotton pledget, and any communicating fibers from the lower lumbar ganglions are severed during this process. As soon as the hypogastric nerves are reached, each is clamped and divided proximal to the clamp; the segment of nerve may then be removed.

In doing subtotal denervation of the bladder, Learmonth employed the transperitoneal route. The bladder is identified, and the upper portion of its fundus is freed extraperitoneally, so that it can be used later as a tractor. The peritoneum is then opened, and the lateral wings of a self-retaining retractor are adjusted. The highest possible Trendelenburg position gives the best exposure for the subsequent steps of the operation. The peritoneum is incised along the course of each ureter and from this point downward to the ureterovesical juncture. The lower ends of these peritoneal incisions are then joined in front of the rectum. Various methods of identifying the nerves may be used. Learmonth does it by making a dissection toward the lateral wall of the pelvis, until the sheath of fascia on the internal aspect of the pelvic blood vessels is identified, when the dissection is deepened in this plane. The ganglion and its branches lie against the inner aspect of this fascia, and by carrying out the dissection in this way the vesical nerves can be identified. The five or six larger nerves for the lateral aspect of the bladder are in turn picked up by a hook and divided. When both sets of nerves have been divided, the procedure is repeated on the remaining side. Hemorrhage has not been a factor during these manipulations.

[ED. NOTE.—Neurosurgical procedures in urology are an innovation of the last decade. Renal denervation as practiced by Legueu, Papin and others is well known. Grant's contribution is noteworthy, although the indications for its employment will be limited. Learmonth, in the treatment for certain types of vesical paresis, has made a distinct advance. When the detrusor function is active to some degree, by section of the presacral nerve, the brake on the emptying mechanism of the bladder may be released. Just what remains to be accomplished in this field is as yet difficult to determine, as too few patients have been treated at the present time to warrant drawing conclusions.]

Grant,⁵¹ following the experience of Spiller and Frazier, advised chordotomy for relief from pain in the genito-urinary tract. Chordotomy

51. Grant, F. C.: Cordotomy for Relief of Pain in the Genito-Urinary Tract. *J. Urol.* 25:551 (June) 1931.

has three definite advantages over posterior rhizotomy and other surgical measures proposed for relief from pain. By section of the spinothalamic tract, anesthesia for pain can be obtained over the entire contralateral half of the body up to within one or two segments of the level of the incision. If the posterior roots exposed in the operative field are also cut, the area of anesthesia may extend up to the same segment. Motor function is not impaired following chordotomy; only pain and temperature sensations are destroyed, whereas touch, position and muscle sense remain intact. Chordotomy requires the removal of only three spines and laminae, thus reducing the operative risk. The fourth thoracic segment is the level at which the section should be made. In this region the cord is easily exposed and because of its relatively small size may be rotated readily for proper placing of the incision.

Chordotomy for relief of pain has been performed in 49 cases by Frazier or his associates. Grant reviewed only the 13 cases in which the lesion producing pain involved the genito-urinary tract. Six of the patients were men, and the remainder were women. The average age was 50 years. Twelve patients had carcinomatous growths involving the genito-urinary tract, and 1 patient suffered from ulcers of the bladder. All required morphine before operation to control the pain. Three patients succumbed as a direct result of the operation. These data illustrate the value of chordotomy for the relief from severe intractable pain in the pelvis and lower extremities. In every instance the pain ceased promptly, and morphine was no longer required.

UROGRAPHY

Herbst⁵² stated that pyeloscopy preliminary to pyelo-ureterography will eliminate repeated cystoscopic examination if urograms are unsatisfactory as a result of difficulties in filling technic. There are definite renal abnormal motility syndromes that produce pain which can be recognized by pyeloscopy and satisfactorily relieved by physostigmine (eserine) or sympathectomy. The further observations and medical and surgical data obtainable in this field offer a new era in the handling of syndromes of renal pain.

Pettit and Dunham⁵³ stated that patients with renal tuberculosis are usually intolerant of instrumentation, because of their extreme sensitiveness. Ureteral catheterization should be avoided if possible, especially as it may be necessary to give a general anesthetic for this proce-

52. Herbst, W. P.: Pyeloscopy: A Diagnostic Procedure Which Promises to Inaugurate a New Era in the Recognition and Satisfactory Treatment of Painful Abnormal Motility Syndromes of the Upper Urinary Tract, *J. Urol.* **26**:233 (Aug.) 1931.

53. Pettit, R. T., and Dunham, R. W.: Intravenous Pyelography in Renal Tuberculosis, *Radiology* **17**:113 (July) 1931.

ture. Ascending pyelography should also be avoided if possible. Kearns reserves retrograde urography for cases in which diagnosis is doubtful, and does not inject kidneys in the presence of advanced cavernous disease because of danger of rupture into the renal substance. Patients with renal tuberculosis should not be subjected to unnecessary shock.

A method that will visualize the urinary tract without the necessity of a general anesthetic, shock of instrumentation and dangers of dissemination is desirable in treating renal tuberculosis. Intravenous urography has been successfully employed by Pettit and Dunham in 5 cases. No untoward results, contraindications or harmful effects were noted. They concluded that intravenous urography is safe and painless in renal tuberculosis, and that it may reveal surprising anatomic changes. A careful study of a larger number of cases, utilizing this method in conjunction with the older chemical, functional, bacteriologic and anatomic methods will greatly increase the knowledge of this disease.

URINARY DISEASES IN PREGNANCY

Crabtree and Prather⁵⁴ accept as a working hypothesis that pelvic and ureteral overdistention exists in all pregnant women as a direct result of a tight-fitting fetus in an inelastic abdomen. Changes in renal pressure occur as a rule at or near the end of the fourth month. Stasis in the pelvis and ureters is present from the fifth month to the end of pregnancy. The right kidney is affected more frequently than the left, regardless of the position of the fetus. Cystoscopic and pyelographic evidence shows that immediately after delivery there is atony of the pelvic and ureteral musculature. The pelvis remains for a time distensible beyond the normal capacity of the renal pelvis, whereas forcible overdistention produces the typical deformity of pyelonephritis in pregnancy. All these factors usually return to normal near the end of the third month after delivery, these retrogressive changes taking place in proportion to the degree and duration of overdistention.

The symptoms of urinary disease in pregnancy are confusing. Cystitis is rarely encountered even when infected urine has been passing through the bladder for months. Symptoms of pyelonephritis are the most common, irrespective of the underlying lesion. Renal tuberculosis which has its inception during pregnancy may simulate or it may be pyelonephritis. Later the colon bacillus disappears, and the bacillus of tuberculosis both in stains and guinea-pig tests are produced.

Treatment of urinary infection during pregnancy is as follows: As a preventive measure, the importance of high intake of fluid is stressed.

54. Crabtree, E. G., and Prather, G. C.: *Urinary Diseases in Pregnancy: A Consideration of Preventive and Therapeutic Measures in Treatment and Conservation Surgery*, *J. Urol.* 26:499 (Oct.) 1931.

If any pains referable to the kidneys or fever appear, rest in bed is prescribed and fluids are forced to 4,500 cc. a day. When the symptoms disappear, the patient is referred to the urologic clinic. If these cases are uncomplicated by stone or other lesions, the patients usually have no further trouble. High intake of fluid is second in importance to rest in bed. Liquids are administered by mouth when possible, and by rectum and hypodermically in large quantities. A toxic patient seems best carried on from 60 to 80 grains (3.9 to 5.2 Gm.) of potassium citrate, or other alkali, each day. The patients are kept on 40 grains (2.6 Gm.) of methenamine, U. S. P. and 80 grains of acid sodium phosphate throughout pregnancy. If temporary improvement is followed by recurrence of symptoms, or if the elevation of temperature persists for from five to seven days, cystoscopic treatment is instituted. This consists of draining and washing the pelvis with a solution of boric acid, allowing drainage for from fifteen to twenty minutes and installing from 3 to 5 cc. of 1 per cent solution of silver nitrate. The inlying catheter is not needed.

The care of urinary disease after delivery is extremely important. Symptoms are often latent, and infection will exist for six months to a year after delivery before cystitis is evident. The ureters are seldom dilated unless there is a definite stricture, nor is pelvic lavage, as a rule, used in the first three months post partum. If pyuria or bacilluria persists beyond the fourth month, a complete cystoscopic examination is made. Many interesting anomalies and cases suitable for plastic operation and other corrective measures are noted in this group. Some cases show only atony from extreme degree of overdistention. Other pregnancies are inadvisable before complete recovery from the infection has taken place.

Wilhelm⁵⁵ reported a case of postpartum bilateral pyoureter and pyonephrosis with blood high in nitrogen in daily treatment with reflux pelvic lavage gave satisfactory results. This treatment is simple, and applicable in cases of pyoureter and pyonephrosis when reflux can be demonstrated by cystographic examination.

Kretschmer⁵⁶ stated that the types of lesions of the urinary tract occurring in infancy and childhood closely parallel the types found in the adult, except benign hypertrophy of the prostate gland and malignant disease of the prostate gland and bladder. In certain instances, examination revealed the presence of serious destructive lesions of the kidney, which might have been cured had an early diagnosis been made and treatment instituted. Diagnosis and treatment may be carried out as

55. Wilhelm, S. F.: Reflux Pelvic Lavage, *J. Urol.* **26**:247 (Aug.) 1931.

56. Kretschmer, H. L.: Diseases of the Urinary Tract in Infancy and Childhood, *Surg., Gynec. & Obst.* **53**:129 (Aug.) 1931.

for the adult. The cooperation of general practitioner, pediatrician and urologist would lead to examination of these patients in the early stages of the disorder, and thus give them the benefit of proper treatment, and prevent destruction of vital organs.

Levinson⁵⁷ reviewed 25 cases of gangrene of the scrotum of children, including 2 cases of his own. The youngest patient was aged 5 days; the oldest, 14 years. The mortality in cases of gangrene of the scrotum of all types and all ages reported in the literature varies between 22.1 per cent in Coenen and Przedbroski's series to 32.1 per cent in Randall's series. In the 25 cases among infants and children, 17 patients (68 per cent) recovered, 7 (28 per cent) died and for 1 patient (4 per cent) the result was not stated.

There is no standard treatment for gangrene of the scrotum. Chlorinated soda is used with satisfactory results.

The causes of gangrene of the scrotum are usually divided into four groups: (1) infectious diseases, such as measles, influenza, malaria, pneumonia, typhoid fever, variola and varicella, and metabolic diseases, such as diabetes; (2) urinary extravasation and infiltration; (3) trauma to the genital organs or to the buttocks, caused by mechanical, chemical or thermal factors, and (4) local inflammation.

Young⁵⁸ stated that the phenolsulphonphthalein test of renal function is most valuable in showing early impairment, and that it is particularly important to forewarn a surgeon if prostatectomy is contemplated. Chemical changes in the blood usually demonstrate renal changes at a later stage, but when viewed in conjunction with the phenolsulphonphthalein test, they are of great value. Indigo carmine, although valuable in the cystoscopic detection of ureteral orifices if cathetrization is difficult and in giving an idea of the renal function of both sides, is not as accurate as the phenolsulphonphthalein test, nor so accurate as an index of operability in prostatectomy. For more correct determinations of the phenolsulphonphthalein test, a new rotating disk colorimeter and a new system of charting have been designed.

Caldwell, Marx and Rowntree⁵⁹ performed experiments to ascertain the effect of renal sympathectomy in animals. Two dogs were placed in metabolism cages and fed a constant amount of milk, water and dog biscuits. The output of urine was measured daily. After a few days denervation was done through a median line incision, exposing the

57. Levinson, A.: Gangrene of the Scrotum in Infants and in Children. *Am. J. Dis. Child.* **41**:1123 (May) 1931.

58. Young, H. H.: Kidney Function Tests: A New Phthaleinometer and Chart for Recording Tests, *J. Urol.* **26**:25 (July) 1931.

59. Caldwell, J. M., Jr.; Marx, Hellmut, and Rowntree, L. G.: Renal Function After Bilateral Denervation of the Kidney in Normal Dogs, *J. Urol.* **25**:351 (April) 1931.

kidneys through a transperitoneal approach. Sympathetic nerves were removed from the renal artery and vein by dissection. Apparently there was no advantage in sectioning the splanchnic nerves. The renal function was observed by special tests over a period of five months. The dogs remained in good health through the experiment.

Marked polyuria followed denervation in two animals. Transient glycosuria appeared in the first days after denervation in two of the three animals. Concentration of sugar in the blood was not increased, which showed that the glycosuria was renal in origin and might have been due to trauma. Denervation did not impair the capacity of the normal kidney to secrete dye, as indicated by the phenolsulphonphthalein tests. The concentrative power of the kidneys, as shown by the concentration test, was lessened for a time in all, and persisted in one animal for about two months. The response of the kidneys to intake of water was increased more than normal after denervation. The response to a specific diuretic was an increased output by all animals after denervation, and this persisted in one animal for about two months. Overfunction of the kidneys could not be demonstrated at the end of five months in any of the dogs.

Bumpus⁶⁰ made a comparative study of the value of specific gravity of urine with the excretion of phenolsulphonphthalein obtained from each kidney separately in 145 cases. In 99 cases, the tests of specific gravity corresponded with those in which phenolsulphonphthalein was used and were comparable to the known clinical data. There was an average accuracy of approximately 70 per cent, provided the test with phenolsulphonphthalein and the clinical estimate were accurate. Bumpus concluded that the test of specific gravity is an aid in diagnosis, but does not exceed in accuracy the test with phenolsulphonphthalein.

Diathermy in Nephritis.—Ewig⁶¹ presented an analysis of the effect of diathermy on renal function and reported two cases of acute nephritis in which diathermy had produced benefit. He concluded that diathermy of the normal kidney leads to increased diuresis, acute glomerular nephritis is influenced materially by intense diathermy to the kidneys and eclamptic conditions usually disappear without any other therapeutic measures if diathermy is given to the kidneys and to the head. In sub-chronic and chronic nephritis, the results are questionable. The cerebral symptoms of renal insufficiency are influenced favorably by diathermy applied to the head.

60. Bumpus, H. C., Jr.: Tests of Function of Each Kidney Separately: A Comparison of the Value of Specific Gravity of Urine with Excretion of Phenolsulphonphthalein, *J. Urol.* **25**:387 (April) 1931.

61. Ewig, W.: Diathermiebehandlung der Nierenentzündung, *Deutsche med. Wchnschr.* **57**:51 (Jan. 9) 1931.

UROLOGIC SURGERY IN EUROPE

Walters⁶² stated that in urologic clinics in Germany, it is estimated that, following removal of renal calculi, the incidence of recurrence is approximately 10 per cent. Operation for the removal of renal calculi is consequently almost necessarily conservative, and the kidney is preserved. Even large, branched stones can be removed successfully by upward retraction of the renal parenchyma, allowing larger exposure of the renal pelvis. Frequently, temporary nephrostomy is done. In contraction of the vesical neck, von Lichtenberg prefers a transvesical plastic operation, the principle of which is similar to that of Heineke-Mikulicz method of enlarging the pylorus. It consists of splitting the vesical mucous membrane to the mucous membranes of the urethra, enlarging the outlet, and at the same time affording union of mucous membrane to mucous membrane.

In chronic pyelonephritis, if symptoms persist in spite of drainage of the pelvis by ureteral catheter or lavage, exploration of the kidney has seemed warranted. At the time of the exploration, perirenal and peri-ureteral fat is removed, the kidney is decapsulated and temporary nephrostomy is carried out. This procedure promotes better drainage and an increase in the blood supply to the kidney by removal of the constricted fibrous and fatty capsule and by nephropexy. It also affords an opportunity for thorough exploration of the kidney and upper third of the ureter.

The Learmonth operation of resection of the presacral nerve is being used for relief from pain due to extensive carcinomas of the prostate gland, as well as for the treatment for some of the motor disturbances of the bladder. The treatment of vesical neoplasm seems to be becoming standardized. Vesical lesions localized to the dome or lateral walls of the bladder are removed by segmental resection of that portion of the wall of the bladder that contains the lesion. If the tumor is of the localized, papillomatous type with a small noninvolved pedicle, transvesical excision is carried out, approximating the wall of the bladder from the interior. Lesions involving the base of the bladder are destroyed by diathermy. If the tumor involves a large part of the bladder, especially if the ureters are dilated from being obstructed, bilateral inguinal ureterostomy is done, followed later by total cystectomy.

In the majority of cases prostatectomy is done in two stages, with an interval of two or three weeks or longer between cystostomy and prostatectomy, depending on the condition of the patient. In Germany it was observed that a relatively small number of patients operated on for prostatic hypertrophy was more than 70 years of age.

62. Walters, Waltman: Urologic Surgery in Some Foreign Clinics. *Proc. Staff Meet., Mayo Clin.* 6:408 (July 8) 1931.

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SODIUM AMYTAL

ANALYSIS OF INTRAVENOUS USE IN ONE HUNDRED AND SEVENTY-TWO SURGICAL OPERATIONS *

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Sodium amytal is the sodium salt of iso-amyl-ethyl barbituric acid. Barbituric acid derivatives have been used for years by pharmacologists and physiologists as hypnotics and occasionally as anesthetics. Fredet and Perlis were the first to succeed in inducing general anesthesia in man with compounds of this series. The preparation of sodium amytal in pure form, and in a sterile ampule together with a companion ampule of sterile distilled water sufficient to make a 10 per cent solution, enabled investigators to use in man a barbiturate producing general anesthesia by the intravenous route, that had been used successfully for several years in animal experimentation. In February, 1929, Zerkas and MacCallum published the first report of such a study.

Our interest in sodium amytal was aroused by the possibility of:

(1) Inducing a general anesthesia by a more direct method than with the inhalation anesthetics in which the lungs bear the brunt of the administration.

(2) Greater ease of administration and more pleasant, when compared to the gases, as far as the patient is concerned.

(3) The few hours of postoperative oblivion that carries the patient over an exceedingly trying period.

(4) The production of a better general anesthetic than we are accustomed to obtain with nitrous oxide and oxygen, even if combined with the latter, and producing a "balanced anesthesia," in which the burden of anesthesia is placed partly on the preliminary medication and partly on the general anesthetic.

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* From the Department of Surgery, University of Michigan.

* Sodium amytal was supplied by the Lilly Research Laboratories.

DOSAGE AND ADMINISTRATION

In the calculation of the dosage for this series of cases, an attempt was made to obtain the full anesthetic effect of sodium amytal consistent with safety. In view of the fact that the lethal dose for man is as yet unknown, a maximum dose of 1.6 Gm. was maintained, as suggested by the originators. A basis of 20 mg per kilogram of body weight was set as a standard for the average person. Considering the individual variation in the effect of all hypnotics, age, general strength and debilitation were factors in determining the exact amount given some patients, the old and debilitated usually having their calculated dosage decreased from 150 to 300 mg., while young, robust persons were occasionally given from 100 to 200 mg. more. Again, if during the administration of the sodium amytal the blood pressure or the respiratory rate decreased more than usual or the patient dropped off to sleep quicker than usual, the total dosage was decreased from 100 to 300 mg.

The drug was given in our special anesthetic rooms, intravenously at the rate of 1 cc. of the 10 per cent solution per minute. A careful check on blood pressure, respiration and pulse was taken every minute during the administration and every

TABLE 1.—Operations Performed

Herniorrhaphy	22
Appendectomy	16
Cholecystectomy	13
Posterior gastro-enterostomy	12
Operations on the brain.....	11
Plastic operation on the face.....	8
Partial gastrectomy	7
Colostomy	6
Nephrectomy	5
Pyelolithotomy	5
Nephropexy	5
Exploratory laparotomy	5
Resection of colon for cancer.....	4
Subtotal thyroidectomy	4
Resection of glands of neck.....	4
Miscellaneous	44
Total operations	172

The youngest patient was 13 years; the oldest 79.

five minutes during the operation. The veins used frequently became thrombosed. No sloughing at the site of injection occurred.

In all cases preliminary medication consisted of morphine sulphate, $\frac{1}{8}$ to $\frac{1}{4}$ grain, with atropine sulphate, from $\frac{1}{200}$ to $\frac{1}{150}$ grain, given from one-half to one hour before the injection of the sodium amytal.

INDUCTION

As the drug was slowly injected, in from three to five minutes the patients passed gradually, quietly and surely into what appeared to be a normal deep sleep. No stage of excitement was observed. The pupils contract early and will not react to light. At first the patient can be aroused by a needle prick or shaking. As the administration is continued, these stimuli become less effective to a point simulating profound anesthesia.

PULSE, RESPIRATION AND BLOOD PRESSURE

During the administration of sodium amytal, the pulse rate increased in 124 cases an average of 15 per minute; in 25 cases there was an average decrease of 12 per minute; in 23 cases there was no change.

In 100 cases the respiratory rate increased an average of 5.7 per minute; an average decrease of 4.3 per minute occurred in 31 cases. There was no change in 41 cases. The patient's color remained good if an effort was made to keep the upper respiratory passage unobstructed by holding up the jaw and inserting a breathing tube.

A fall in blood pressure occurred in 166 cases during the administration of the drug, the average systolic reduction being 27 mm. of mercury, while the average diastolic reduction was 15 mm. of mercury. Six cases showed a slight tendency toward increase in both systolic and diastolic pressures. There was distinctly less change in the patient's blood pressure if it was normal before the administration of the anesthetic, while persons with hypertension or hypotension showed a much greater reduction. The ordinary operative trauma was a decided stimulus to the return of the blood pressure to normal. The administration of any one of the gases on hand, nitrous oxide-oxygen or carbon dioxide, was much more effective in causing the blood pressure to return to normal than was ephedrine. Sodium amytal had no tendency to keep the blood pressure of a patient with hypertension low during the operation, even though there was a decided reduction during the administration of the drug. In such cases the pressure usually rose higher during the operation. For example, in one case (no. 231429) the blood pressure varied thus: before operation, 160 systolic and 70 diastolic; during administration of anesthetic, 90 systolic and 74 diastolic, and during operation, 200 systolic and 100 diastolic.

DURING OPERATION

As a routine the operation was started within from three to five minutes from the time of completion of the administration of the drug. Into the skin and parietal peritoneum a local anesthetic was usually injected before incision. No inhalation anesthetic was given until requested by the surgeon because of (1) occasional poor relaxation, (2) a tendency for the patient to squirm under the stimulus of the incision, or (3) handling of the viscera.

Sodium amytal alone was entirely satisfactory in 42 of the cases. In 21 cases of this group major abdominal operations were performed. The intestines appeared to be collapsed and could be packed away from the operative field with more than the usual ease. Exposure was ideal. There was no increased tendency toward bleeding or oozing. Facilities for closure were perfect. The effect lasted well beyond the average time for the operation.

The remaining 130 cases required an additional anesthetic agent as shown in table 2.

In the 2 cases in which added open ether was used plastic operations were performed on the face requiring analgesia, the selection being made for convenience only. Greater relaxation was the need for adding a low grade ether vapor to the nitrous oxide and oxygen in 11 cases; in 6 of these cases the calculated dose of sodium amytal had been diminished. Accordingly, in at least 119 of 130 cases, the demand was for analgesia alone, the sodium amytal supplying the other qualifications of a good anesthetic.

The administration of nitrous oxide and oxygen was started in proportions of about 90 to 10 per cent at any time needed, and in the great majority of cases was rapidly reduced to 75:25 or lower, with satisfactory results. It could be stopped and restarted at any time during the

TABLE 2.—*Supplementary Anesthesia Used*

	Cases
Nitrogen monoxide-oxygen 90/10 per cent-75/25 per cent.....	112
Nitrogen monoxide-oxygen plus low grade ether vapor.....	11
Open ether	2
Local	4
Avertin	1
Total cases	130

operation without the patient waking up. Hyperventilation of the lungs was carried out at the end of each operation with carbon dioxide and oxygen.

Of 121 abdominal cases the relaxation was entirely satisfactory, almost to the extent of an open ether anesthesia, in 112. In 7 of the remaining 9 cases, the calculated dose of 20 mg. per kilogram was reduced from 100 to 500 mg. In this attempt to study the full value of sodium amytal as an anesthetic, we felt that the last 100 to 300 mg. of the drug added greatly to the depth of the narcosis and the degree of relaxation.

Considering the anesthesia as a whole, 160 cases were declared to be entirely satisfactory to the operating surgeon. In 6 of the remaining 12 cases, major abdominal operations were performed in which the calculated dose of sodium amytal had been decreased. During a laparotomy, in spite of the full dosage of sodium amytal supplemented by nitrous oxide and oxygen, the patient squirmed about during the whole operation. In the remaining 5 cases, in which operations on the brain were performed, there was a tendency to move the head during the operation, which was extremely disconcerting.

IMMEDIATE POSTOPERATIVE COURSE

All the patients were placed on full special or half special nursing care until they had completely reacted from the sporific effect of the drug. Special nursing was then continued or discontinued according to the general need of the patient. The blood pressure was taken every twenty minutes for the first three to four hours and every hour thereafter until the patient had reacted. Rarely did the pressure decrease enough to indicate the use of cardiovascular stimulants, and at no time was it alone a cause for alarm. Deep breathing was encouraged in all patients. In older persons this was stimulated by a few breaths of 5 per cent carbon dioxide and 95 per cent oxygen at twenty-minute intervals.

A careful check was made to determine the length of time required for these patients to react sufficiently to take fluids by mouth. This analysis is shown in table 3.

TABLE 3.—*Time of Reaction*

Hours to React	Number of Cases	Percentage
2-4.....	44	26.4
4-6.....	32	19.1
6-8.....	33	19.7
8-10.....	17	10.2
10-12.....	18	10.8
12-15.....	7	4.2
15-20.....	11	6.6
20-24.....	1	0.6
24.....	4	2.4

} 65.2%
} 86.2%

The longest period required to react was forty-six hours. The average age of patients reacting in twelve hours was 38 years, over twelve hours, 55 years. The great majority of patients, particularly those who had had other anesthetics previously, were enthusiastic in their praise of sodium amytal and readily agreed to have it again if necessary.

POSTOPERATIVE ANESTHETIC COMPLICATIONS

Nausea and vomiting were rarely seen; certainly, in no case in which the disease or added anesthetic would not account for it entirely.

Restlessness and disorientation were rather common findings in the first few hours; in only three cases, however, did they occur to a degree that could not be adequately handled by the special nurse and the usual postoperative narcotic treatment.

Blurring of vision was noted in two patients at intervals for the first twelve hours.

Fifty-nine of the women and 58 per cent of the men required postoperative catheterization, following the usual standing order for the surgical wards that all patients be catheterized every eight hours after

operation unless they voided voluntarily, and more frequently if more than 10 ounces (295.7 cc.) of urine was obtained. Seventy-six of the patients were catheterized only once or twice. In the whole group, 2 cases of pyelocystitis developed; in both cases herniorrhaphy had been performed, the eight hour, 10 ounce rule was not observed, and the bladder was allowed to overdistend.

The prolonged drowsiness, shallow respirations and lethargy seen in these patients for a variable number of hours postoperatively would seem to add another factor in the production of postoperative infections of the respiratory tract. In 11 of our cases (6.4 per cent) definite pulmonary complications developed following abdominal operations.

TABLE 4.—*Pulmonary Complications*

Age	Operation	Sodium Amytal per Kilogram Body Weight	Supple- mentary Anesthesia	Complications
63	Posterior gastro-enterostomy for duodenal ulcer	17.1 mg.	N ₂ O-O ₂	Bilateral broncho- pneumonia
40	Colostomy, cancer of rectum.....	20.0 mg.	N ₂ O-O ₂	Acute bronchitis
60	Incision and drainage of appendical abscess; bronchopneumonia	15.0 mg.	None	Terminal bilateral bronchopneumonia
39	Repair of ruptured ventral hernia; low grade bronchopneumonia	15.0 mg.	N ₂ O-O ₂	Bronchopneumonia; no worse
48	Repair of inguinal hernia.....	20.0 mg.	N ₂ O-O ₂	Pulmonary edema
62	Cholecystogastrostomy for cancer of head of pancreas	15.4 mg.	None	Bilateral broncho- pneumonia
79	Excision; cancer of the lip.....	17.0 mg.	None	Bilateral broncho- pneumonia
47	Cholecystectomy for cholelithiasis...	15.7 mg.	N ₂ O-O ₂	Bronchopneumonia
60	Exploratory, for cancer of stomach	19.5 mg.	None	Bronchopneumonia left base
19	Repair of bilateral inguinal hernia..	20.0 mg.	N ₂ O-O ₂	Bronchopneumonia, right base
34	Posterior gastro-enterostomy for duodenal ulcer	18.4 mg.	N ₂ O-O ₂	Pulmonary edema

This incidence is not higher than the average in such a group and compares favorably with the incidence in this clinic with other anesthetics, as follows: series 93, ether cases, pulmonary complications, 14 (15 per cent); series 96, ethylene, pulmonary complications, 4 (4.2 per cent), and series 172, sodium amytal, pulmonary complications, 11 (6.4) per cent.

There were no deaths in this series directly attributable to the use of sodium amytal.

CONCLUSIONS

1. Sodium amytal given intravenously is a satisfactory addition to the anesthetic armamentarium.

2. It is an exceedingly agreeable form of anesthesia from the patient's point of view.

3. In consideration of the fact that 75 per cent of the patients required an additional anesthetic, we raise the question as to whether smaller doses of sodium amytal plus the additional anesthetic would not be just as satisfactory as our nearly maximal dose. This would effect a decrease in the length of time of postoperative narcosis and its consequent possible complications.

PATHOGENESIS OF HYPERNEPHROMA *

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From the numerous reports in the literature on hypernephromas, it is apparent that much confusion exists concerning both the clinical course and the pathologic variations. It is commonly believed that the hypernephroma is a highly malignant tumor and runs a rapid course. Such a concept is at variance with our findings.

We have studied a group of forty-four instances of hypernephroma observed at the Montefiore Hospital, in which autopsies were obtained in thirty-three. In the remainder, pathologic diagnoses were based on the examination of removed kidneys or on biopsies from metastases. Of this group, twenty-eight showed clinical manifestations of neoplasm. In the remaining sixteen, a hypernephroma was discovered as an accidental observation at autopsy. Such tumors were limited solely to a kidney or a suprarenal gland. The patients in this group presented no clinical evidence of a hypernephroma, and all died of other unrelated diseases in which the tumor played no apparent rôle.

The term hypernephroma is applied to neoplasms of the kidney or the suprarenal gland that are yellowish and vascular, that show a tendency toward hemorrhage, necrosis and cyst formation, and that microscopically resemble in some areas the structure of the suprarenal cortex. Histologic examination of sections from different areas of such tumors reveals marked variation in the structure and arrangement of the cellular elements. Much of the confusion in the literature has arisen from attempts to limit the criteria of hypernephromas to the tumors presenting the characteristic microscopic resemblance to the suprarenal cortical tissue. Ewing excluded from this group tumors with distinct lumina and those showing papillary structures.

Since the classic description of hypernephromas by Grawitz, a prolonged and difficult controversy as to the pathogenesis and mode of development has taken place. It is beyond the scope of this paper to discuss at any length the evidence for the origin of hypernephroma.

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whether from the cortical suprarenal rest (Grawitz,¹ Chiari,² Beneke,³ Pick,⁴ Schmorl,⁵ Askanazy,⁶ Lubarsch,⁷ Gatti,⁸ Kelly⁹ and Gerlach and Gerlach¹⁰ or from the cells of kidney tubules (nephrogenic origin as developed by Stoerk¹¹). (For a complete review of the literature see Lubarsch.⁷)

Stoerk and his school based their conclusions as to the nephrogenic origin of hypernephroma on certain histologic resemblances of the individual cells and their arrangement to renal tubular epithelium. Considerable weight is added to his theory by the frequent association of papillary and adenomatous structures in true Grawitz tumors.

The adherents of the suprarenal origin of these tumors base their conclusions on the close similarity of the arrangement and appearance of the cells of the tumor to those of the fascicular layer of the cortex of the suprarenal gland and the frequency with which hypernephromas are found at the sites in the kidney where suprarenal cortical rests are common.

Pick described an instance of a ganglioma and hypernephroma in the same tumor in the kidney. The development of this unique tumor arose, in his opinion, from a suprarenal rest in the kidney containing both cortical and medullary tissue. He concluded, therefore, that this is *prima facie* evidence in support of the suprarenal origin of hypernephromas.

Gerlach and Gerlach, in a review of ten Grawitz tumors, seven suprarenal rests and three carcinomas of the kidney, concluded that the new growths arise from cortical rests. According to these observers, cortical adenomas develop from aberrant suprarenal rests. The adenoma undergoes further hyperplasia and differentiation into a hypernephroma, at first benign and then malignant. The malignant hypernephroma may assume various histologic appearances. In the same tumor may be found papillary or adenomatous structures, or the tumor may resemble a diffusely infiltrating sarcoma or carcinoma. They

1. Grawitz, Paul: Virchows Arch. f. path. Anat. **93**:39, 1883.
2. Chiari: Ztschr. f. Heilkund., 1884, vol. 88.
3. Beneke, R.: Beitr. z. path. Anat. u. z. allg. Path. **9**:440, 1891.
4. Pick, L.: Med. Klin. **23**:3 (Jan. 7) 1927.
5. Schmorl: Beitr. z. path. Anat. u. z. allg. Path., 1891, vol. 9.
6. Askanazy, M.: Beitr. z. path. Anat. u. z. allg. Path. **14**:133, 1893.
7. Lubarsch, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologische Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6.
8. Gatti, G.: Virchows Arch. f. path. Anat. **144**:467, 1895.
9. Kelly, A.: Beitr. z. path. Anat. u. z. allg. Path. **23**:280, 1898.
10. Gerlach and Gerlach: Zur Histogenese der grawitschen Tumoren der Niere, Beitr. z. path. Anat. u. z. allg. Path. **60**:383, 1915.
11. Stoerk, O.: Beitr. z. path. Anat. u. z. allg. Path. **43**:393, 1908.

expressed the belief that all these elements may arise from the same cells, and that these variations are stages in a continuous development.

Lubarsch, though favoring the suprarenal origin of hypernephromas, expressed the opinion that the papillary structures in hypernephromas are due to the growth of inclusions of kidney tubules in the anlage of the suprarenal rests which are secondarily stimulated to growth by the development of the hypernephroma. He preferred the expression hypernephroid tumor and included in this group all the hypernephromas or true Grawitz tumors. Under this term he further subdivided the Grawitz tumors into true hypernephromas, hypernephromatous adenomas, papillary adenomas and hypernephroid carcinomas.

There have been some experimental attempts to reproduce hypernephromas in animals by transplantation of cortical tissue into the kidney. For the most part, the results have been negative and inconclusive because of failure of the transplants to grow (Galleotti and Villasanta.¹²

CASES WITH CLINICAL MANIFESTATIONS

This group of cases consisted of twenty-eight instances with definite symptoms or physical signs of neoplasm. An autopsy was obtained in nineteen. In the other nine instances, a pathologic diagnosis was made by the examination of excised tissue.

The age of onset varied from 35 to 70 years, the greatest number occurring in the fifth and sixth decades. The duration of illness from the initial symptom to death ranged from six months to twenty-two years. The average duration of life after the onset of the initial symptoms was four years and four months.

The most frequent mode of onset was with urinary manifestations, such as frequency, tenesmus, nocturia, inability to void and hematuria. Abdominal pain or pain in the lumbar region was the initial complaint in a few cases. In some instances no symptoms were noted until a mass was accidentally discovered during the course of an examination, and in a few cases loss of weight and weakness were the first observations.

Very often metastatic lesions constituted the earliest evidence of disease. In some patients a pathologic fracture due to a metastatic lesion was the first indication of the presence of a malignant disease (case 10). In one instance, the first symptoms were those of a brain tumor (case 8). Especially interesting is the group of cases that masqueraded as primary tumors of the pelvic bones (cases 7, 15, 16,

12. Galleotti, Villasanta, Pandi and Imbert, quoted by Lubarsch (footnote 7).

18 and 24). One patient was treated during a period of eight years for a primary giant cell sarcoma of the ilium. This diagnosis was made on the basis of a biopsy (case 15). In one instance, the patient complained of pain in the chest and a cough for seven years prior to the onset of urinary symptoms. This was due to the presence of a pulmonary metastasis (case 20).

TABLE 1.—*Observations in Twenty-Eight Cases*

Case	Name	Sex	Age	Initial Symptoms	Operation
1	Schweig.....	Female	44	Metastases to spine with cord symptoms	Nephrectomy
2	Barsky.....	Female	53	Urinary symptoms	Nephrectomy
3	Friedland.....	Male	71	Painful abdominal mass and ascites	
4	Leon.....	Male	46	Urinary symptoms	Nephrectomy
5	Kerner.....	Male	57	Urinary symptoms	Nephrectomy
6	Marcus.....	Male	39	Metastases of pelvis and left femur	
7	Felber.....	Male	53	Bone metastases	
8	Markowitz.....	Female	53	Brain tumor	
9	Altman.....	Female	48	Urinary symptoms	Nephrectomy
10	Jacobs.....	Male	54	Bone metastases	
11	Levine.....	Male	50	Urinary symptoms	Nephrectomy
12	Grauer.....	Male	52	Urinary symptoms	Nephrectomy
13	Weichler.....	Male	66	Urinary symptoms	Nephrectomy
14	Bernstein.....	Male	70	Cord symptoms	
15	Kerling.....	Male	55	Tumor of right ilium	
16	Silverman.....	Male	51	Tumor of right ilium	
17	Leventhal.....	Male	53	Urinary symptoms	Nephrectomy
18	Block.....	Female	54	Bone metastases	
19	Epstein.....	Male	35	Metastases to chest	Nephrectomy
20	Hellenthal.....	Male	62	Metastases to chest	
21	Heyman.....	Male	51	Urinary symptoms	Nephrectomy
22	Kleinerman.....	Female	44	Loss of weight, asthenia	
23	Leder.....	Male	55	Urinary symptoms	
24	Mayer.....	Male	44	Tumor of right hip	
25	Goldkoff.....	Female	46	Urinary symptoms	Nephrectomy
26	Ruff.....	Male	53	Urinary symptoms	Nephrectomy
27	Cruzius.....	Female	59	Vaginal bleeding	
28	Gross.....	Female	60	Urinary symptoms	

Modes of Onset

A. Urinary symptoms:

1. Urgency
2. Frequency
3. Hematuria
4. Tenesmus
5. Inability to void

B. With pain, either abdominal or lumbar, or both

C. With the discovery of a mass in the abdomen

D. With evidence of metastatic symptoms:

1. As a tumor of the pelvis
2. With metastases to the chest or bone metastases
3. With metastases to the chest or bone metastases
4. With metastases to the chest or bone metastases

E. With loss of weight and cachexia

Another unusual method of onset is with vaginal bleeding (case 27). Such cases have been previously described (Gellhorn¹³). This symptom is due to invasion of the vaginal wall by retrograde extension of tumor tissue into the vaginal veins from the inferior vena cava.

RESULTS OF TREATMENT

In thirteen cases nephrectomy was performed. The duration of life following nephrectomy varied from one year and one month to

13. Gellhorn, G.: Zentralbl. f. Gynäk. 53:527, 1929; Am. J. M. Sc. 156:94, 1918.

seven years, with an average duration of two years. The efficacy of nephrectomy in this group of cases cannot be estimated, because all the cases had a fatal termination.

Since only about 50 per cent of cases of hypernephroma of this series began with symptoms that led to investigation of the kidneys, nephrectomy was performed only in this group. In the other group, the initial symptoms were those due to metastases and precluded the possibility of nephrectomy. A nephrectomy is rarely performed in such cases. The benefit of nephrectomy on the course of the disease is, therefore, extremely difficult to evaluate.

Roentgen therapy was of slight value, in only a few instances relieving the pain due to metastases of the bones or lungs.

TABLE 2.—*Distribution of Metastases as Determined by Autopsy and Roentgen Examinations*

No. of Cases		No. of Cases	
No metastases.....	15	Ribs.....	3
Retroperitoneal nodes.....	6	Heart.....	3
Suprarenal gland.....	6	Peritoneum.....	5
Lung.....	20	Thyroid.....	3
Left renal vein.....	1	Pancreas.....	3
Inferior vena cava.....	1	Diaphragm.....	1
Skull.....	5	Brain.....	3
Pelvis.....	10	Duodenum.....	2
Femora.....	7	Humerus.....	3
Skin.....	4	Spleen.....	1
Liver.....	3	Cervical nodes.....	1
Spine.....	3	Uterus.....	1
Spinal cord.....	2	Gallbladder.....	1
Opposite kidney.....	2	Small intestine.....	2
Sternum.....	2		

GROUP OF CLINICALLY UNDIAGNOSED HYPERNEPHROMAS (ACCIDENTAL FINDING)

This group is composed of sixteen cases, in fourteen of which the tumor arose in the parenchyma of the kidney, and in two, in the suprarenal gland. The ages of these patients varied from 23 to 79 (table 3). In none were there any symptoms or physical signs referable to the hypernephroma. The diameter of the tumors varied from 2 to 12 cm. These tumors resembled, both macroscopically and microscopically, the tumors found in patients with clinical manifestations of hypernephroma.

The tumors that were chance findings at autopsy illustrate all gradations and transitions from benign suprarenal cortical adenomas in the kidney or suprarenal gland to highly malignant hypernephromas. Various sections from the same tumor may show all these gradations (cases 32, 39, 42 and 44). The presence of benign cortical adenomatous tissue, malignant hypernephroma cells, alveolar structures and papillary

formations are all found in the same tumor in different areas. This point has been emphasized by Gerlach and Gerlach,¹⁰ Bothe¹⁴ and Ljunggren.¹⁵

By the ordinary criteria of a malignant condition, some of these tumors resemble the most malignant tumors. It is of significance that such highly malignant tumors may reach considerable size without presenting any clinical manifestations. Since a large portion of kidney tissue may be destroyed without impairment of function or without erosion into the pelvis, the tumor may attain considerable size before causing symptoms.

TABLE 3.—Group of Undiagnosed Hypernephromas (Accidental Findings)

Case	Name	Sex	Age	Primary Diagnosis*	Site and Size
29	H. H.	Female	79	C. A. C. V. D.; arteriosclerosis.....	Lemon-sized
30	J. M.	Male	63	Cardiac insufficiency; arteriosclerosis...	Left kidney, melon-sized
31	G. R.	Male	67	Generalized arteriosclerosis; hypertrophy of prostate; bilateral hydro-nephrosis	Right kidney, small
32	L. F.	Female	52	Scoliosis, after laminectomy.....	Left kidney, 4 cm. in diameter
33	F. R.	Male	68	Carcinoma of colon.....	Left kidney
34	S. G.	Female	64	Hypertension; diabetes	
35	M. H.	Male	64	C. A. C. V. D.	Left kidney, 3 by 4 cm.
36	J. R.	Male	78	C. A. C. V. D.; hypertension.....	Left kidney, 2.5 cm.
37	M. G.	Male	23	Diabetes, cystitis	Small nodule
38	J. T.	Male	65	Fibroid phthisis	Left kidney, 2 cm.
39	I. L.	Male	62	Generalized arteriosclerosis; cardiac hypertrophy	Left suprarenal gland
40	L. F.	Male	37	Multiple sclerosis	Left kidney, 9 cm.
41	R. S.	Female	61	Endothelioma of brain.....	Upper two thirds of left kidney
42	L. C.	Male	68	Generalized arteriosclerosis	Left kidney, 7 by 5 by 5 cm.
43	M. L.	Male	70	Carcinoma of esophagus.....	Left kidney, pea-sized
44	M. F.	Male	24	Hypertension	Right suprarenal gland

* C. A. C. V. D. indicates chronic arteriosclerotic cardiovalvular disease.

Case 44 in which there was a malignant tumor of the suprarenal gland, illustrates the probable source of the malignant hypernephroma, for in both suprarenal glands in this patient, in addition to the hypernephroma, were found multiple benign cortical adenomas. It is extremely suggestive, therefore, that the hypernephroma represented a malignant transformation of a benign tumor.

COMMENT

A review of the histopathologic observations of Grawitz tumors emphasizes the marked variation in structure that may occur in the

14. Bothe, A. E.: Ann. Surg. **84**:57, 1926.

15. Ljunggren, E.: Studien über Klinik und Prognose der Grawitzschen Nierentumoren, zugleich ein Beitrag zur Frage nach der Genese der Hämaturie, Acta chir. Scandinav. **66**:1, 1930.

development and growth of a hypernephroma. In many instances all gradations from a benign cortical adenomatous structure to a highly malignant carcinomatous or sarcomatous appearance may be found in the same tumor. In addition, the almost constant occurrence of papillary structure in some areas of the hypernephroma makes any arbitrary classification on the basis of purely morphologic variations useless and unnecessary.

The examination of single sections of a hypernephroma may show a papillary adenomatous arrangement of the cells, and a diagnosis of carcinoma may be made. Further sections from other parts of the same tumor reveals its true nature. Some of the reported instances of carcinoma of the kidney may have been hypernephromas.

The histogenesis of the hypernephroma from cortical aberrant tissue is suggested from a study of the embryology of the suprarenal gland and the kidney. The cortical tissue of the suprarenal gland and the areas of the epithelial mesoderm from which the kidney develops lie closely together in embryonic life. Though the suprarenal cortex is developed from the mesothelium of the wolffian ridge in common with the ovary or the testis and though the kidney develops from the renal blastoma that lies below the suprarenal gland and is separated from it by the wolffian body, the suprarenal gland after the second month of fetal life is so closely applied to the kidney that inclusion of cortical tissue in the kidney may readily occur. In the course of development of the renal tissue, a few aberrant cells of the suprarenal tissue may become included in the kidney and remain there. It is probable that such cellular rests may later develop blastomatous characters. Gerlach and Gerlach¹⁰ suggested that indifferent undifferentiated cells of the kidney anlage may be included in the aberrant suprarenal tissue, and that both groups of cells may develop and form the Grawitz tumor.

From our studies the hypothesis of kidney cellular inclusions in the suprarenal rest to account for the variations in structure of a hypernephroma is unnecessary. Transitions from small cells with dense cytoplasm and deeply chromatic nuclei to large foamy cortical cells may be distinguished. This is illustrated most strikingly in case 39, a hypernephroma arising in the suprarenal gland, in which the question of nephrogenic cellular inclusions is excluded. In this instance, some of the tumor cells are typical hypernephroma cells and others are cuboidal cells resembling epithelial cells. There can be no doubt that these cells are of the same origin. The dense chromatin content of the nuclei and the sparse cytoplasm of the cell with an absence of the lipoid material of cytoplasm are clearly distinguishable. The cuboidal cells have lost their characteristic arrangement and are grouped around cystlike and alveolar spaces. Similar variations occur in hypernephromas of the kidney.

The frequency of areas showing benign cortical adenomatous structures in a highly malignant hypernephroma (cases 39, 44, 2, 18 and 28) emphasizes the probable development of a malignant hypernephroma from a benign hyperplasia of a cortical rest in the kidney. In case 28, the primary tumor showed a highly malignant hypernephroma with striking pleomorphism. In the metastases in the pancreas, the tumor has a benign appearance with large blood spaces throughout the nodule. This development is analogous to the malignant transformation of adenomatous tissue in the thyroid, as emphasized by Marine.

If this concept is true, the life cycle of the hypernephroma must of necessity be extremely long. The cortical rest in the kidney, congenital in origin, may at any time in the life of the patient undergo adenomatous growth and develop into a more rapidly growing or malignant tumor. There probably are periods of arrest of such growths. This makes it almost impossible to determine the age of hypernephromas. It is partly for this reason that so large a group of accidental findings of hypernephromas may occur.

The intimate relationship between the hypernephroma and its extensive vascular supply permits an early metastatic dissemination by rupture into the thin-walled veins that are present in such numbers in the tumor. It is probable that in the cases in which metastatic lesions were present for years the metastases occurred at a stage of relatively low malignancy of the primary tumor. This is entirely analogous to certain types of thyroid carcinomas that histologically may appear adenomatous in structure with metastases of similar benign microscopic appearance. This type of tumor in the thyroid is notoriously slow in its growth and may even show histologic evidence of function.

SUMMARY

An analysis, from a clinical and pathologic point of view, of forty-four cases of hypernephroma is presented. In sixteen of these, the tumor was a chance observation at autopsy.

The neoplasm may exist for many years prior to the onset of symptoms.

There is extreme variation in the interval between the onset of symptoms and the death of the patient from the neoplasm.

In about half of the cases the primary symptoms of neoplasm were referable to metastatic lesions, such as those of the pelvis, skull, long bones, vagina and lungs.

The existence of a primary malignant neoplasm of the kidney with metastatic foci may exist for some time prior to the development of any symptoms.

All gradations from a benign structure to a malignant hypernephroma were found in the same tumor.

All types of histologic variations may occur in the same tumor, such as a cortical adenoma, a typical hypernephroma, papillary and adenomatous forms and highly malignant carcinoma and sarcoma-like infiltrations.

Comparative studies emphasize the histogenetic development of a hypernephroma from cortical aberrant tissue. Cortical suprarenal rests in the kidney may grow into benign adenomas. At any period during the life of the patient, such benign structures may become malignant. This development and subsequent metastatic dissemination proceeds at a variable rate.

APPENDIX

Histopathology.—A brief description of the histology of the tumors described is given in the following cases.

CASE 1.—S. S., a woman, aged 44, was admitted to the hospital on June 4, 1923. Her symptoms began about four years before admission with pain in the lumbar region. There were no urinary symptoms. On June 20, 1921, nephrectomy of the left kidney was performed, and also a splenectomy because of involvement of the spleen. Eighteen months after the onset, weakness of the left leg developed.

The patient died on Jan. 14, 1924.

Autopsy revealed a recurrent hypernephroma at the operative site with metastases to the peritoneum, spine and lung, compression myelitis, chronic cystitis and right pyelonephritis. The left suprarenal gland was destroyed.

Section through the primary tumor showed, in some areas, the structure of a typical hypernephroma, and in other areas, papillary formation (fig. 1).

CASE 2.—M. B., a woman, aged 53, was admitted to the hospital on June 4, 1923. Her illness began twenty-two years before admission with attacks of pain in the left loin associated with hematuria. Seven years prior to admission a mass developed in the left flank, and the patient was operated on, nephrectomy of the left kidney being performed because of a hypernephroma. Three years before admission she noticed a nodule in the left submaxillary space. Three months prior to admission lumps developed in the left side of the neck, and one month later she began to cough and had dyspnea.

Roentgen examination of the chest showed metastatic involvement.

The patient died on Jan. 14, 1924.

Autopsy revealed a recurrent tumor in the left kidney region, with metastases to the lungs, liver, spleen, right kidney, suprarenal glands, right and left, bronchi, mediastinal and retroperitoneal lymph nodes, heart, small intestine, mucous membrane of the gallbladder, the skin and the cervical and axillary nodes.

On section through a lymph node, some areas showed the structure of a typical hypernephroma. In other areas, the nuclei were much larger than usual. Other sections showed typical papillary structure.

Section through the recurrent tumor at the site of nephrectomy showed an extreme degree of malignancy with no resemblance to the typical hypernephroma, and only slight evidence of papillary structure. The tumor consisted of large numbers of irregular cells, loosely packed with very little stroma. There was

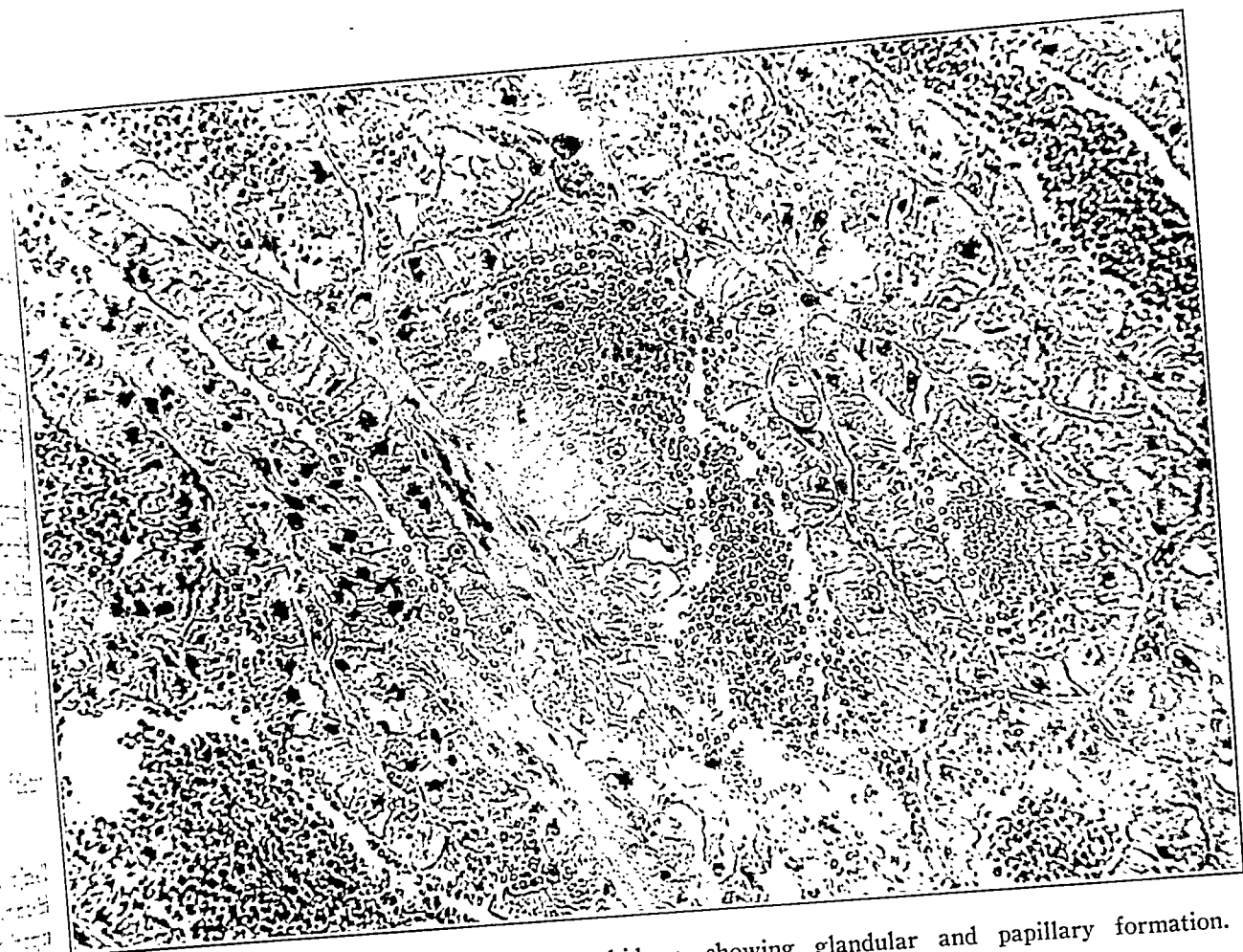


Fig. 1 (case 1).—Section through the kidney, showing glandular and papillary formation. Reduced from a magnification of $\times 240$.



Fig. 2 (case 2).—Section through lymph node, showing a typical hypernephroma. Reduced from a magnification of $\times 240$.

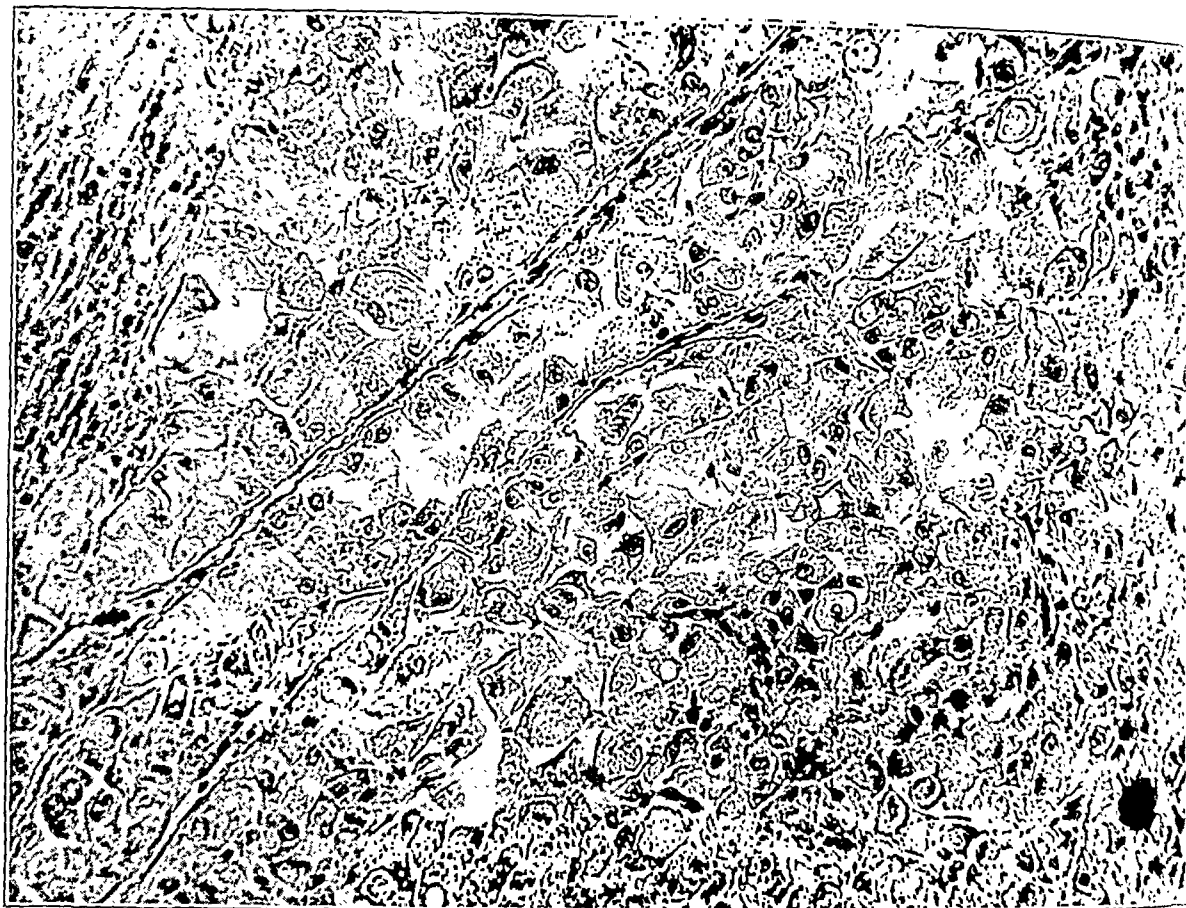


Fig. 3 (case 2).—Section through the recurrent tumor at the site of nephrectomy, showing the highly malignant structure with pleomorphism and a tendency to papillary formation. The hypernephroma character is not evident. Reduced from a magnification of $\times 240$.



Fig. 4 (case 2).—Section through the metastatic lung, showing a predominance of [unclear] structure. Reduced from a magnification of $\times 240$.

marked pleomorphism, with numerous tumor giant cells and large areas of necrosis. In the metastatic lesions, the papillary structure predominated (figs. 2, 3 and 4).

CASE 3.—P. F., aged 71, was admitted to the hospital on Feb. 2, 1916. The illness began six months previous to admission with a dull continuous pain in the iliosacral region, especially the right, with radiation down the thigh. The urine contained faint traces of albumin. Three months later the ankles became swollen, and ascites developed. At this time a mass about the size of a grape fruit was noted in the right lumbar region, with dilated veins over it. The right thigh became swollen.

The patient died on February 12.

Autopsy revealed a tumor of the right kidney, secondarily infected with metastases to the bronchial lymph nodes. The right and left renal veins and the inferior vena cava were thrombosed.

Section through the primary tumor showed a slightly atypical papillary structure with invasion of the blood vessels. The cells were much larger than those of a typical hypernephroma. The cytoplasm was pink-staining. There was a loose arrangement of the cells with marked pleomorphism and the presence of giant cells. The typical hypernephroma structure was not present.

The impression was of a highly malignant hypernephroma. The size of the cells was probably due to the imbibition of water.

CASE 4.—M. L., a man, aged 46, was admitted to the hospital on Feb. 6, 1929. His symptoms began four and one-half years prior to admission with dull pain in the left side, loss of weight and hematuria. In December, 1926, one year after the onset, the left kidney was removed for a hypernephroma. Seven months after operation, a mass recurred in the left kidney region, with hematuria.

The patient died on Sept. 6, 1929.

Autopsy showed a recurrent mass at the operative site with metastases to the lungs, liver and pleura.

Sections from recurrences at the site of nephrectomy showed nodules of cells lying in a loosely arranged connective tissue stroma with evidence of papillary structure, but no definite evidence of a typical hypernephroma.

The tumor in the kidney removed was reported as a hypernephroma.

CASE 5.—C. K., aged 57, was admitted to the hospital on March 3, 1924. The onset of the illness was five years previously with frequency of urination; one year later hematuria and pain in the hypogastrium, radiating to the lumbar regions, developed. In September, 1921, nephrectomy of the right kidney was performed because of a hypernephroma. Two years after operation, cough and dyspnea developed.

Roentgen examination showed metastases to the pelvis.

The patient died on July 25, 1925.

Autopsy revealed metastases in the lungs, suprarenal glands, left kidney, thyroid, skin, pancreas, mesentery, diaphragm, omentum and bronchial lymph nodes.

Section through the primary tumor showed it to be a typical hypernephroma with some degree of pleomorphism. The metastases showed the same structure.

CASE 6.—J. M., aged 39, was admitted to the hospital on April 22, 1928. The illness began one year before admission with progressive weakness and pain in the left thigh and buttocks and the pelvic region.

Roentgen examination of the pelvis showed a neoplasm of the right and left ilia and the upper end of the left femur.

The patient died on August 24.

Autopsy revealed a hypernephroma of the left kidney.

Sections through the primary tumor showed: In places, there were typical papillary adenomatous structures. In other areas, the cells were arranged in a mosaic, with vacuolated cytoplasm and well defined cell membranes. In some sections, the cells showed a marked absence of lipoid material with extreme pleomorphism. There were areas of hemorrhage.

CASE 7.—M. F., aged 53, was admitted to the hospital on July 22, 1926. The onset of the illness was eleven months before admission with sharp pain over the right seventh rib and pain in the right lumbar region. Examination revealed a cystic mass over the seventh rib and a mass in the left lumbar region. Three weeks before admission to the hospital, hematuria was noticed.

Roentgen examination revealed metastases to the lungs, skull and ribs.

The patient died on September 22.

Biopsy of an axillary node showed a structure typical of a hypernephroma.

CASE 8.—S. M., aged 53, was admitted to the neurologic service of the hospital on June 4, 1926, with a six months' history of headache and convulsions. A diagnosis of brain tumor was made, metastatic in character.

Roentgen examination showed involvement of the right humerus and the skull with evidence of increased intracranial pressure.

The patient died on July 7.

Autopsy revealed a hypernephroma of the left kidney, with metastases to the lungs, pancreas, duodenum and thyroid.

Section through the primary tumor showed a typical hypernephroma structure with areas of hemorrhage and necrosis and large cystlike spaces. The metastases in the pancreas showed a striking absence of lipoid material. The nuclei were much larger than in the original tumor and showed marked pleomorphism.

CASE 9.—E. A., aged 48, was admitted to the hospital on June 17, 1926, in a moribund condition, with evidence of a left hemiplegia. Three years before admission the right kidney had been removed because of hematuria, and a hypernephroma was reported to be present.

Roentgen examination showed a pathologic fracture of the right femur and metastases to the pelvis and ribs.

The patient died on June 19.

Autopsy showed a recurrent mass at the operative site with involvement of the regional lymph nodes, ribs and the right suprarenal gland.

There was a typical hypernephroma, with areas of hemorrhage. A slight degree of pleomorphism was present. In the metastases, giant cells with many nuclei were present.

CASE 10.—H. J., aged 54, was admitted to the hospital on Dec. 16, 1927. The onset of the illness was two and one-half years prior to admission with a dull ache in the left thigh followed by a pathologic fracture of the left femur.

Roentgen examination showed metastases of the left femur and the left sacrum. The left kidney was enlarged.

Biopsy of a specimen from the left femur through the neoplasm showed a hypernephroma.

The patient died on Jan. 14, 1928.

CASE 11.—F. L., aged 50, was admitted to the hospital on May 18, 1927. The onset of the illness was about two years before admission, with hematuria. Shortly after the onset, nephrectomy of the left kidney was performed because of a hypernephroma. On admission, roentgen examination showed evidence of a metastatic pulmonary and mediastinal involvement.

A typical hypernephroma was present in the kidney removed.

The patient died on Feb. 3, 1928.

CASE 12.—S. G., aged 52, was admitted to the hospital on Dec. 19, 1927, complaining of headache, weakness, loss of weight, diminished vision, dizziness, vomiting and hemoptysis. The onset of the illness was eighteen months before admission with urinary symptoms. In September, 1926, the right kidney was removed because of a hypernephroma.

Roentgenograms showed metastases to the lungs and areas of absorption in the skull.

The kidney removed was reported to contain a typical hypernephroma.

The patient was discharged from the hospital on Jan. 14, 1928.

CASE 13.—M. W., aged 66, was admitted to the hospital on May 13, 1928. The illness began three years previously with retention and bloody urine. In December, 1927, the left kidney was removed for a hypernephroma. The patient entered the hospital because of paralysis of both legs, evidence of a compression myelitis and a nodule in the thyroid.

Roentgenograms showed metastatic involvement of the fourth dorsal vertebra.

The kidney removed was reported to contain a typical hypernephroma.

The patient was discharged from the hospital on June 2, 1928.

CASE 14.—B. B., a man, aged 70, was admitted to the hospital on July 5, 1928. The onset of the illness was four months before admission with evidence of compression myelitis. He complained of inability to use his legs and of incontinence of urine and feces. Examination revealed a mass over the thoracic spine and the lower ribs.

The patient died on September 9.

Autopsy showed a hypernephroma of the right kidney with local extension and invasion and metastases to the spinal cord.

The hypernephroma was typical with areas of hemorrhage and necrosis. In some areas there was papillary formation with some degree of pleomorphism of the nuclear elements. There was capsule formation around the tumor.

CASE 15.—A. K., a man, aged 55, was admitted to the hospital on Feb. 1, 1929. The illness began eight years previously with pain in the right buttock radiating down the right thigh and swelling of the right hip. He received roentgen therapy to the right hip, a diagnosis of endothelioma having been made. Six months before admission, masses had developed on the sternum, the right axilla and in the skull, the latter pulsating.

The patient died on April 3.

Autopsy revealed a hypernephroma of the right kidney with metastases to the left kidney, sternum, ribs, cranium, right ilium and ischium, pubis, lungs and right suprarenal gland.

Section throughout the tumor of the kidney showed a typical hypernephroma. There were several adenomas in the right suprarenal gland.

CASE 16.—B. S., aged 51, was admitted to the hospital on Aug. 6, 1929. The onset of the illness was fifteen months before admission with pain in the right hip, right leg and foot. About five months prior to admission a swelling of the right hip developed.

The patient died on Feb. 8, 1930.

Autopsy showed a hypernephroma of the right kidney with metastases to the lungs, right ilium and sacrum.

Section through the kidney showed a typical benign suprarenal adenomatous structure with a slight degree of pleomorphism of the nuclear elements. In places there were large irregular spaces with areas of hemorrhage. In another section, the cells were less polyhedral and more cuboidal. They formed irregular cystlike

spaces into which the tumor extended as irregular papillary projections. The metastatic lesions had a typical hypernephroma structure.

The hypernephroma showed transitions from a benign to a malignant neoplasm, with variations in the structural arrangement of the cells.

CASE 17.—H. L., aged 53, was admitted to the hospital on Dec. 2, 1928. The onset of the illness was twenty-three months before admission with pain in the left lumbar region, loss of weight and hematuria. Six months later, nephrectomy of the left kidney was performed because of a hypernephroma. Following operation abdominal pain, dyspnea, cough and hemoptysis developed.

Roentgenograms showed metastatic involvement of the lungs and mediastinum and a pathologic fracture of the left seventh rib.

The report of examination of the kidney removed was that of a hypernephroma. The patient died on March 4, 1929.

CASE 18.—S. B., aged 54, was admitted to the hospital on Sept. 12, 1925. The onset of the illness was seven months previously with pain in the right lower extremity and back and loss of weight.

Roentgen examination showed metastatic involvement of the skull, right os pubis and right and left femora.

The patient died on November 22.

Autopsy revealed a hypernephroma of the right kidney with metastases to the lungs.

Sections from the primary tumor in the kidney showed areas of a typical hypernephroma with pleomorphism and hemorrhage. In other sections, the tumor had an adenomatous and papillary structure. In still other sections, the cells of the tumor lay free in a very loose connective tissue stroma. Here the cells showed marked pleomorphism. These areas were definitely demarcated from the more typical hypernephroma tissue by a distinct capsule. In still other areas, the hypernephroma had a definitely benign appearance, the structure closely resembling cortical adenoma. This case, like case 31, showed all gradations from benign to malignant hypernephroma, papillary adenomatous structure and highly malignant invasive carcinoma-like tissue (figs. 5 and 6).

CASE 19.—M. E., a man, aged 35, was admitted to the hospital on Feb. 19, 1918. The onset of the illness was two years before admission with pain in the right hip and a mass in the left side of the abdomen. Nine months before admission, the left kidney was removed because of a hypernephroma. Five weeks after nephrectomy the patient began to limp, and he complained of pain radiating down the left leg. A swelling developed over the right hip.

The patient died on June 20.

Autopsy revealed a recurrent tumor at the site of the left kidney with metastases to the retroperitoneal, iliac and inguinal lymph nodes, skull, lungs, liver, right ilium and femur and the skin.

The diagnosis was a hypernephroma with papillary structure and extensive necrosis, hemorrhage and formation of cystlike spaces. The recurrent tumor at the site of nephrectomy showed a diffuse, loosely arranged, cellular mass with very little stroma. The cells were large and irregularly round and showed marked pleomorphism.

There was a highly malignant structure in the recurrent tumor.

CASE 20.—B. H., aged 62, was admitted to the hospital on July 4, 1918. The illness began seven years before admission with pain in the right side of the chest

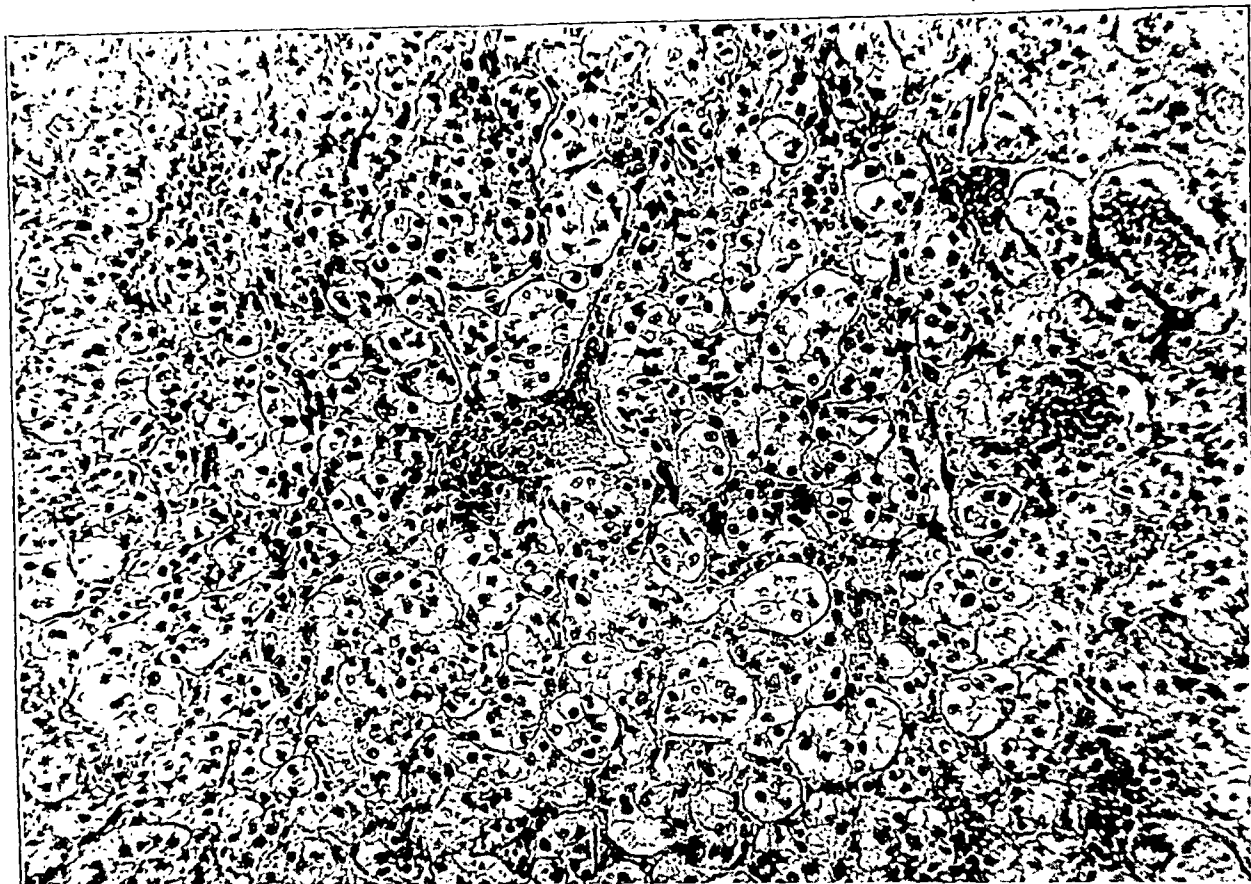


Fig. 5 (case 18).—Section through the primary tumor, showing a benign hypernephroma. Reduced from a magnification of $\times 240$.

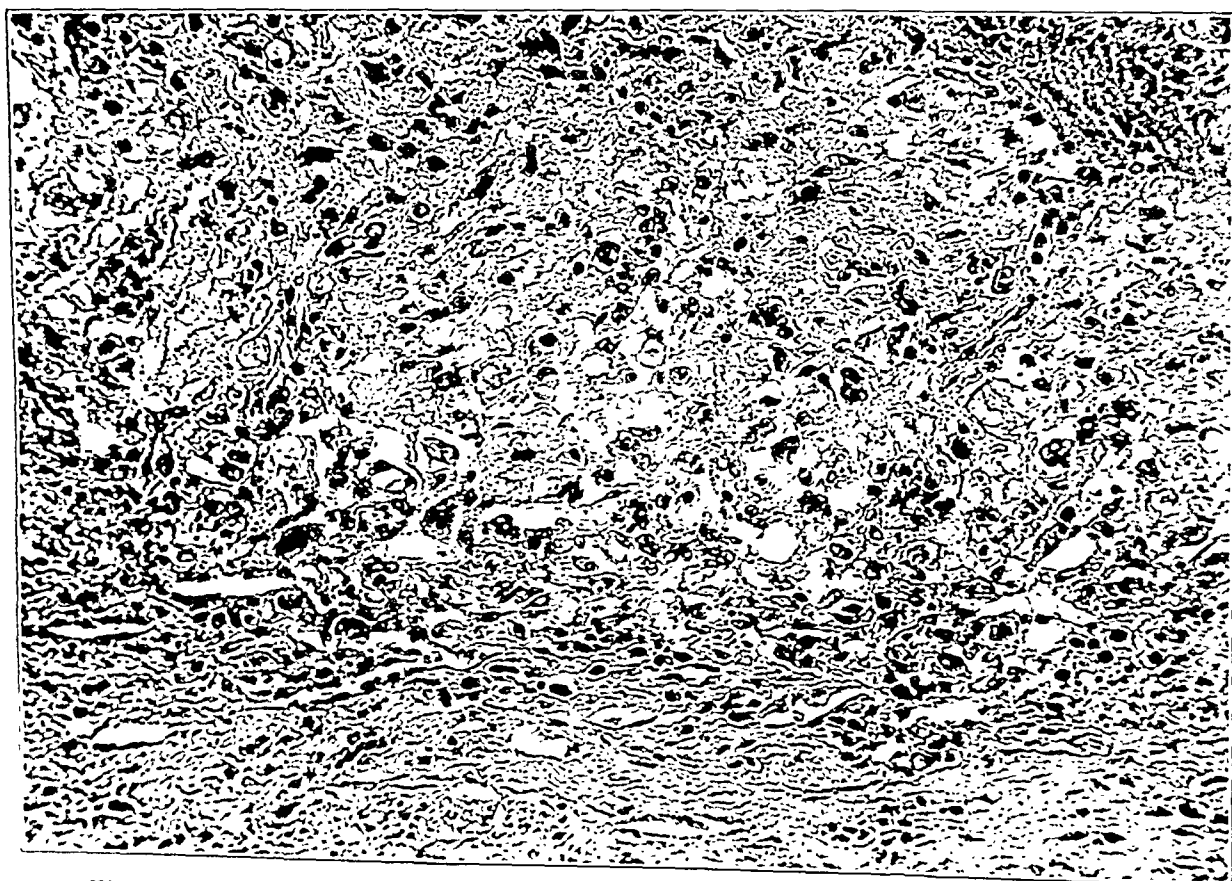


Fig. 6 (case 18).—Another section through the same tumor, as in figure 5, showing a highly malignant structure, resembling a carcinoma. Reduced from a magnification of $\times 240$.

and shortness of breath. Three years prior to admission weakness, loss of weight and appetite, constipation and abdominal pain developed. One year later the patient noticed dysuria and hematuria.

Roentgen examination showed a dense shadow in the lower lobe of the right lung and apical infiltrations.

The patient died on November 13.

Autopsy revealed a hypernephroma of the right kidney with pulmonary metastases.

Section of the tumor showed a typical hypernephroma.

CASE 21.—L. H., aged 51, was admitted to the hospital on Nov. 30, 1922. The onset of the illness was two years before admission with hematuria. One year after the onset, the left kidney was removed because of a hypernephroma. On admission, the patient complained of pains in both lower extremities, difficulty in walking, weakness and loss of weight.

Roentgenograms showed metastatic involvement of the lungs, left ilium and ischium, the neck of the right femur and the ninth dorsal vertebra.

The kidney removed was reported to contain a hypernephroma.

The patient died on December 30.

CASE 22.—M. K., aged 44, was admitted to the hospital on Oct. 29, 1922, with a three months' history of loss of weight, asthenia, cough and expectoration. On examination, a mass was found in the left side of the abdomen.

Roentgen examination of the chest showed a mass in the mediastinum and invasion of the lung. An exploratory operation revealed an inoperable tumor of the left kidney from which a specimen of tissue was removed.

Biopsy of a specimen of the tumor of the kidney removed at operation showed a typical hypernephroma.

The patient died on Jan. 23, 1930.

CASE 23.—Z. L., aged 55, was admitted to the hospital on Aug. 8, 1922. The onset of the illness was eleven months prior to admission with attacks of hematuria. Eight months before admission the patient began to cough; he was admitted to the tuberculosis division with a diagnosis of pulmonary tuberculosis.

The patient died on April 17, 1923.

Autopsy revealed chronic pulmonary tuberculosis, tubercles in the kidney and meninges, tuberculosis of the ilium and colon and a hypernephroma of the right kidney. The bleeding was apparently due to the hypernephroma.

There was an atypical hypernephroma structure with marked pleomorphism of the nuclear elements and some degree of papillary formation. Though the cells were larger than those generally found in the more typical hypernephroma, the general arrangement of these cells in a mosaic with a network of fine connective tissue containing many capillaries definitely established the diagnosis of a hypernephroma.

CASE 24.—A. M., aged 44, was admitted to the hospital on March 6, 1924. The onset of the illness was one month prior to admission with inability to walk, pain in the legs and pain and swelling of the right hip.

The patient died on March 21.

Autopsy revealed a hypernephroma of the right kidney, with metastases to the heart, regional and distal lymph nodes, lungs, left suprarenal gland, right hip and sternum.

Section from the tumor of the kidney showed a typical hypernephroma. There were cystlike spaces and areas of necrosis. In other areas, the hypernephromatous structure was completely replaced by irregular papillary formation, showing

marked pleomorphism of the columnar cells lining the papillae. In still other areas, the tumor had the appearance of a highly malignant invasive sarcomatous structure with areas of necrosis and marked pleomorphism of the cells. In the metastases, the hypernephromatous structure was not present, but the cells were arranged in irregular, solid alveoli, separated by thin septums of connective tissue. Many giant cell forms were present.

The diagnosis was: hypernephroma with extreme variation in structure and arrangement of the cellular elements (figs. 7, 8, 9 and 10).

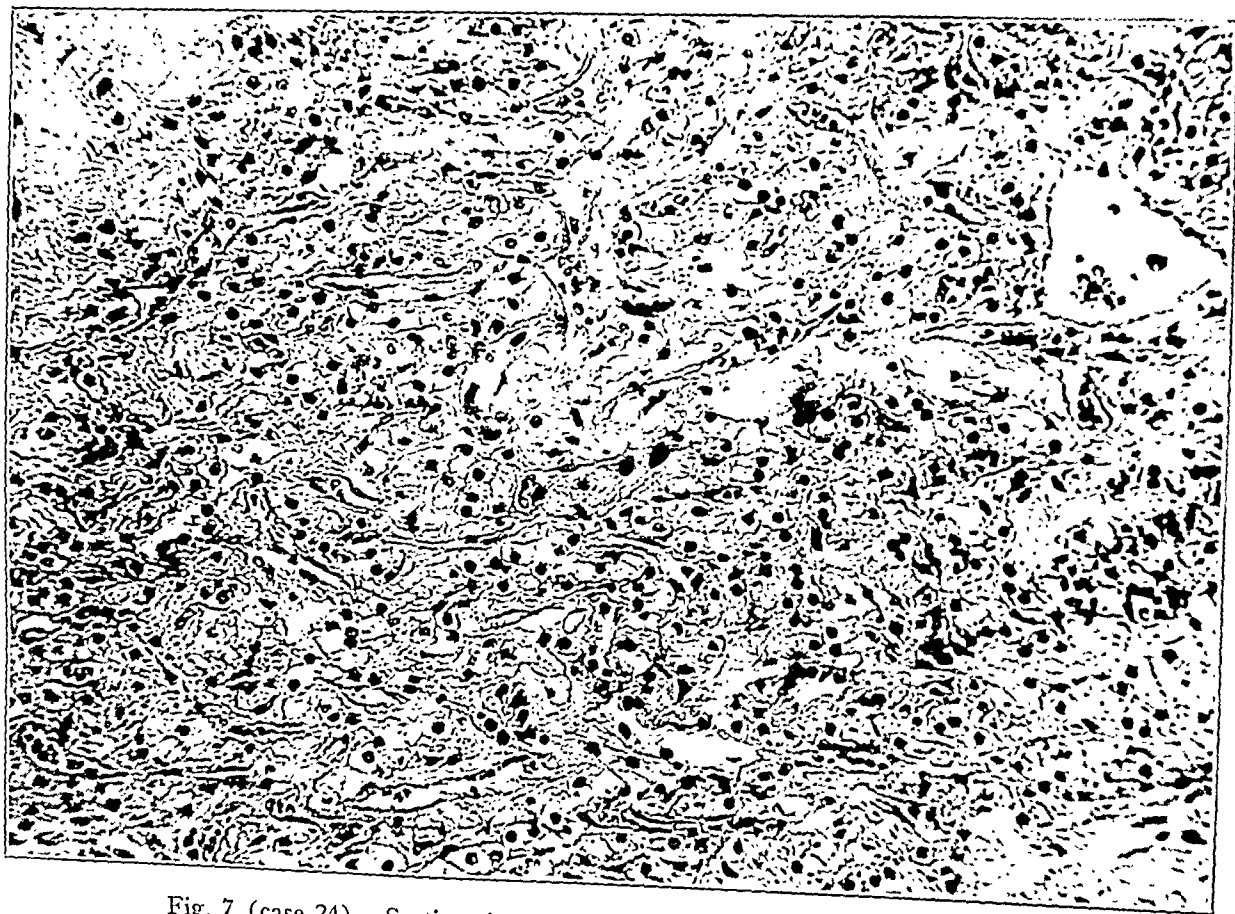


Fig. 7 (case 24).—Section through the tumor of the kidney, showing a typical hypernephroma with small cystlike spaces. Reduced from a magnification of $\times 240$.

CASE 25.—E. G., aged 46, was admitted to the hospital on March 15, 1924. The illness began four years before admission with pain in the left side of the abdomen and urinary frequency. In November, 1922, nephrectomy of the left kidney was performed because of a hypernephroma. On admission to the hospital, there were evidences of local and peritoneal recurrences.

The kidney removed showed a hypernephroma.

The patient died on April 16, 1924.

CASE 26.—D. R., aged 53, was admitted to the hospital on July 1, 1924. The onset of the illness was eighteen months before admission with lumbar pain and hematuria. In June, 1923, the left kidney was removed because of a hypernephroma.

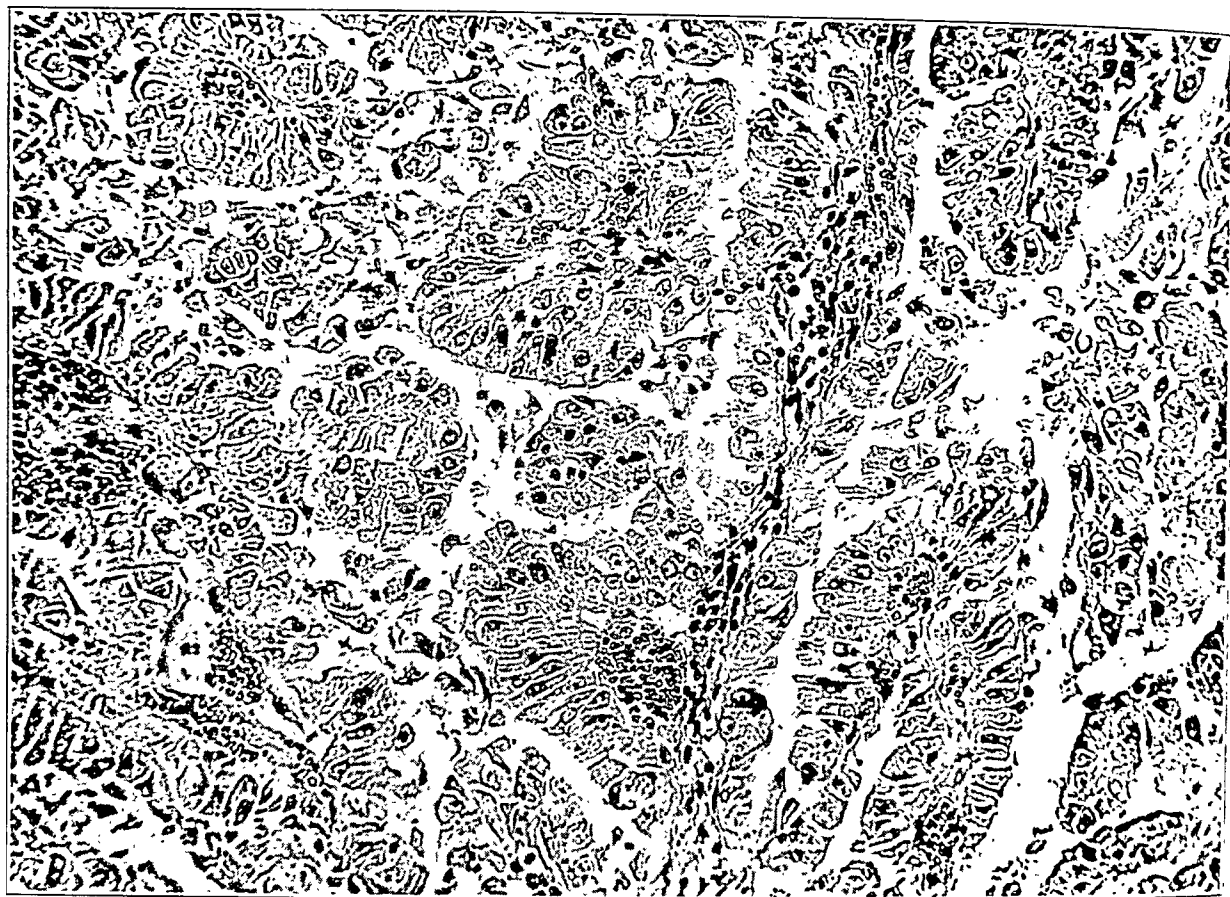


Fig. 8 (case 24).—Section through the same tumor as in figure 7, showing papillary formation with pleomorphism of the cells. Reduced from a magnification of $\times 240$.



Fig. 9 (case 24).—Section through the same tumor as in figure 7, showing the highly malignant character of hypernephroma cells. Reduced from a magnification of $\times 240$.

The kidney removed showed a hypernephroma.
The patient died on Dec. 6, 1924.

CASE 27.—C. C., aged 59, complained of vaginal bleeding. On examination, a small friable mass extending from the posterior vaginal wall was found.
Tissue taken for a biopsy from the posterior vaginal walls showed the structure of a hypernephroma.

CASE 28.—R. G., aged 60, was admitted to the hospital on Nov. 14, 1929. The illness began five years prior to admission with hematuria. One month before admission the patient sustained a pathologic fracture of the right femur.

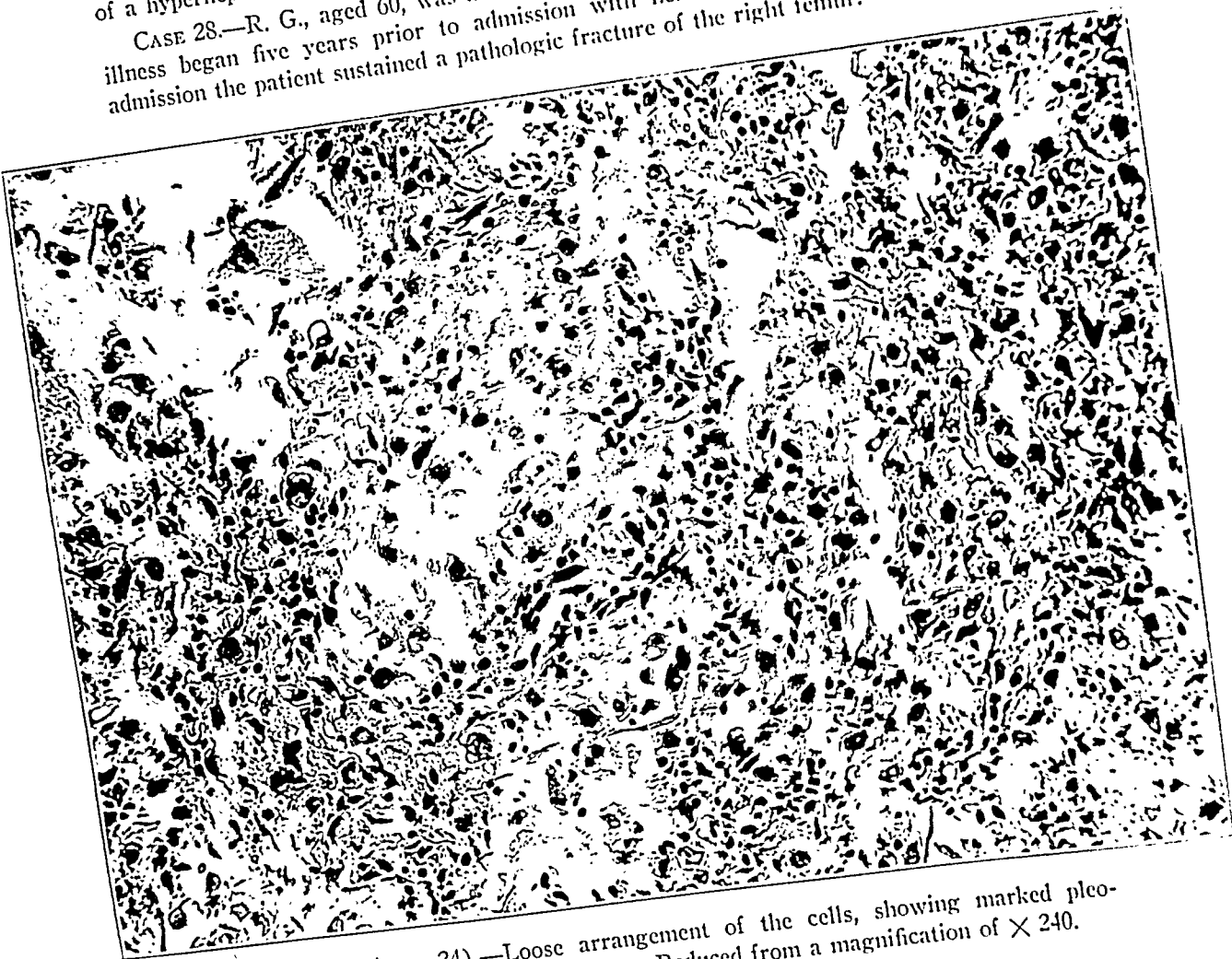


Fig. 10 (case 24).—Loose arrangement of the cells, showing marked pleomorphism and sarcoma-like structure. Reduced from a magnification of $\times 240$.

Roentgen examination showed metastases of the right humerus, the soft parts of the chest and the right femur, with a pathologic fracture.
The patient died on Sept. 15, 1930.

Autopsy revealed metastases of the skin, peritoneum, myocardium, lungs, duodenum, pancreas, ilium, mesentery and thyroid. The right kidney was the seat of a hypernephroma.

In some areas a structure of typical hypernephroma was seen, with marked pleomorphism in other sections. The hypernephroma structure was lost near the edge of the tumor, where the cells grew individually, presenting the picture of a sarcoma with marked pleomorphism. Transitions from the more benign to the

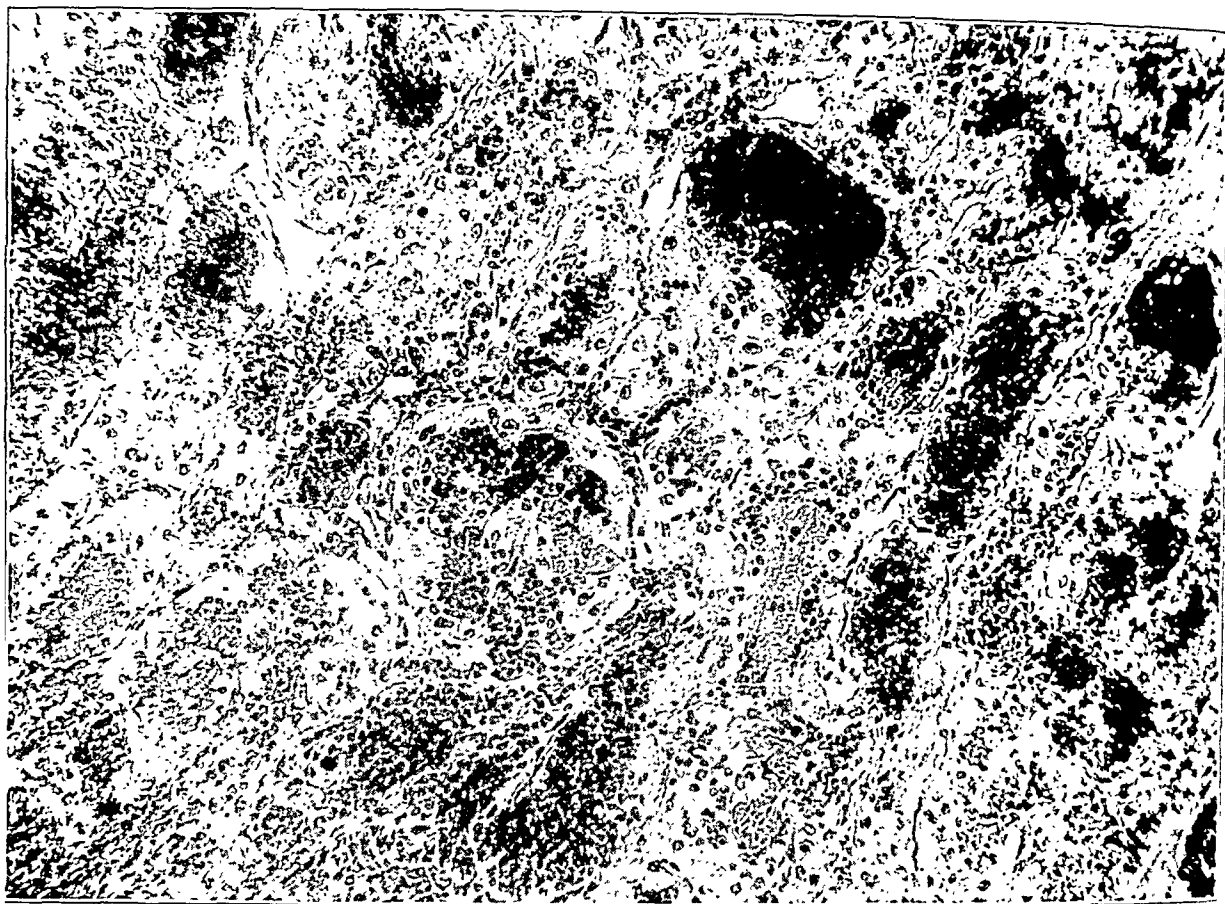


Fig. 11 (case 28).—Section through the metastasis in the pancreas, showing the benign appearance with large blood spaces throughout. Reduced from a magnification of $\times 220$.

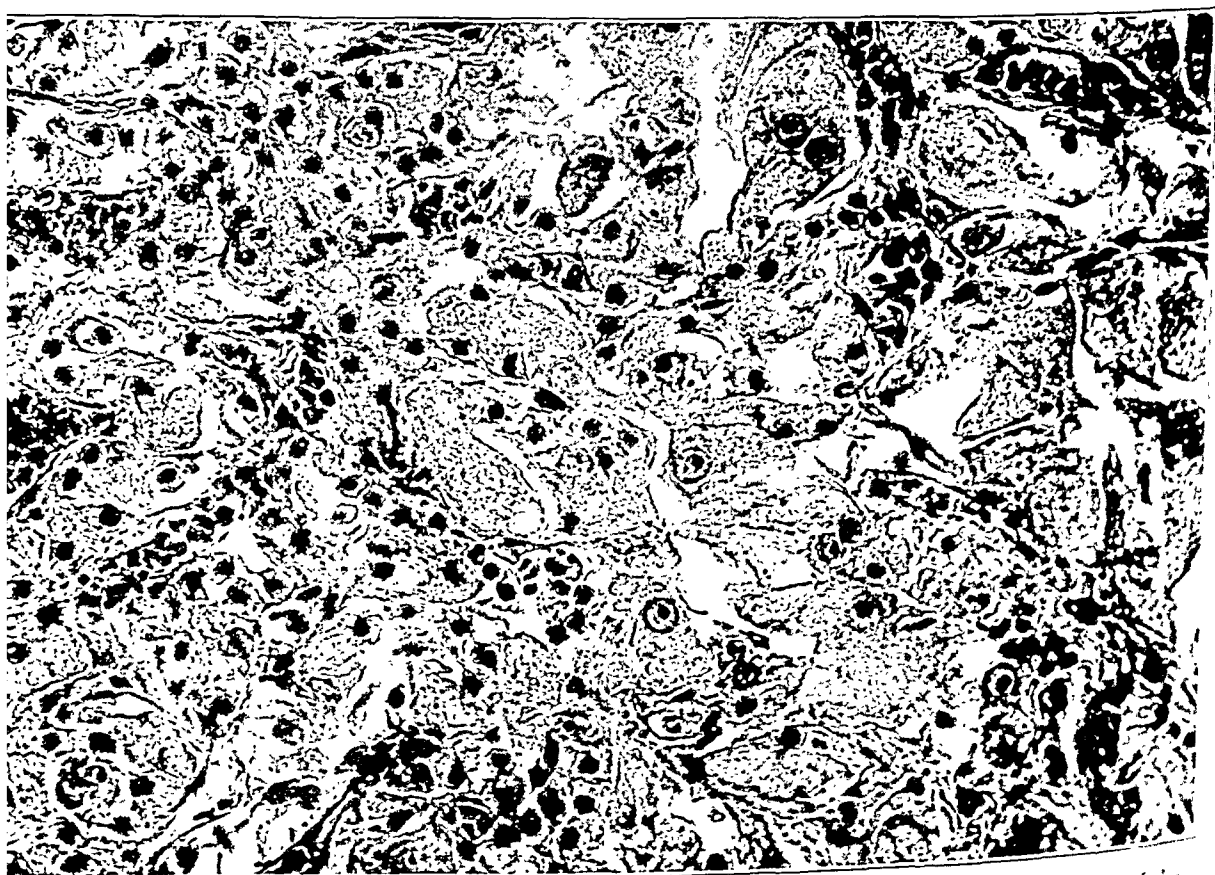


Fig. 12 (case 28).—Section through the edge of the tumor, showing marked pleomorphism of the cells with ganglion-like structure. Reduced from a magnification of $\times 440$.

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highly malignant invading cells were seen. Papillary structures were present in other sections. In the metastases all gradations were present. In the pancreas, the metastases had a benign appearance with large blood spaces throughout the nodule (figs. 11, 12 and 13).

CASE 29.—H. H., a woman, aged 79, who died of arteriosclerotic heart disease, presented a lemon-sized tumor in the left kidney. On section, there were groups of closely packed polygonal cells arranged in strands and sheets with a fine network of capillaries and connective tissue. The nuclei were small, round and eccentric. The cytoplasm was extremely foamy. In other areas, there was a typical papillary structure. The papillae were composed of two or three layers

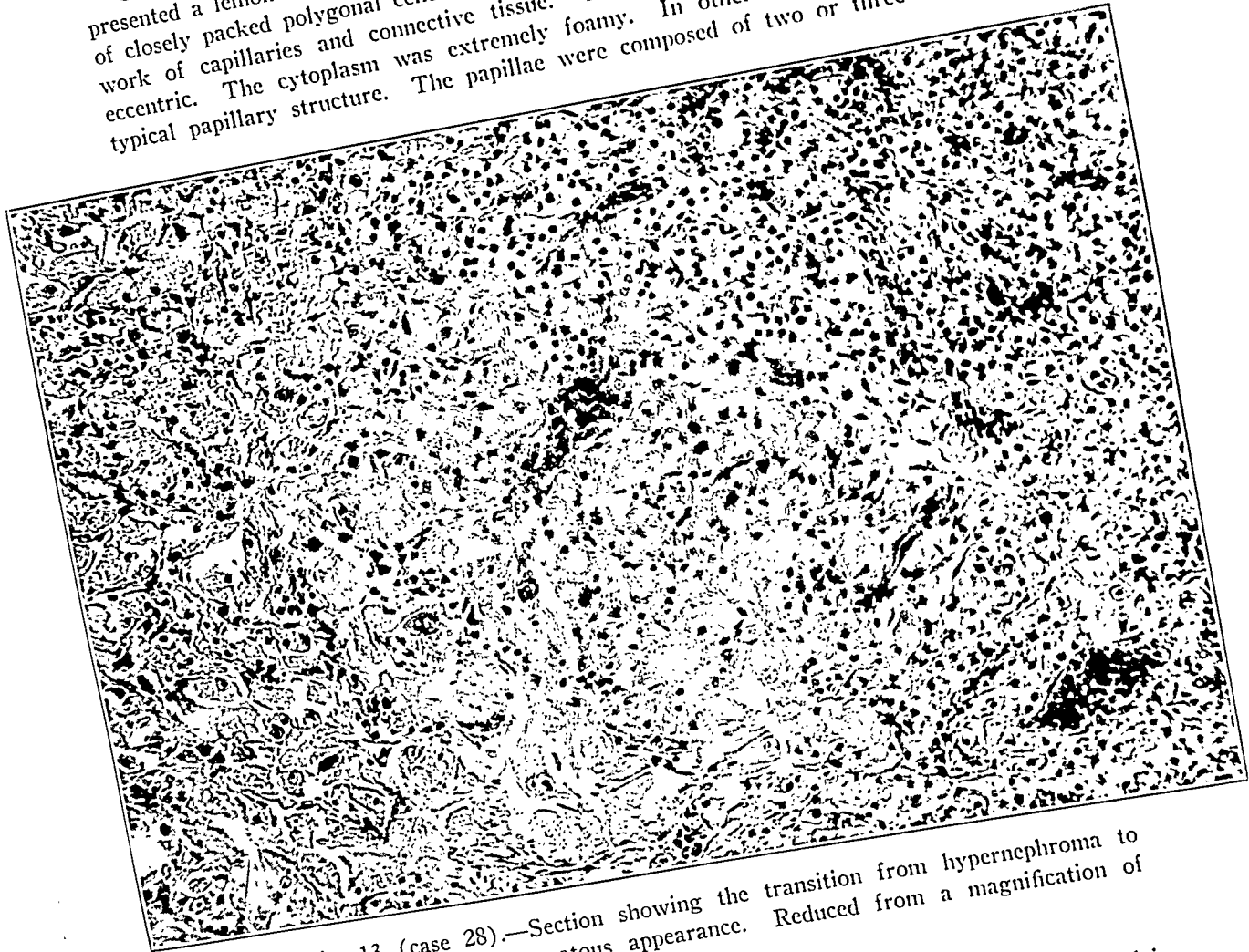


Fig. 13 (case 28).—Section showing the transition from hypernephroma to highly malignant carcinomatous appearance. Reduced from a magnification of $\times 220$.

of cuboidal and polygonal cells lining a fine connective tissue stalk. The nuclei were large and rich in chromatin. There were many cystlike spaces. Some of these contained blood.

Sections from some areas showed the structure of a typical hypernephroma. In other areas the structure resembled that of a papillary carcinoma (figs. 14 and 15).

CASE 30.—J. M., a man, aged 63, who died of cardiac insufficiency and arteriosclerosis, presented a tumor, the size of a lemon, in the left kidney, a typical hypernephroma. The cells were fairly uniform in size, and were arranged in columns and sheets with a fine network of connective tissue containing capillaries.



Fig. 14 (case 29).—Cells arranged as in a typical hypernephroma. The darker staining cells are masses of tumor cells arranged in solid sheets and containing little lipoid material. Reduced from a magnification of $\times 240$.

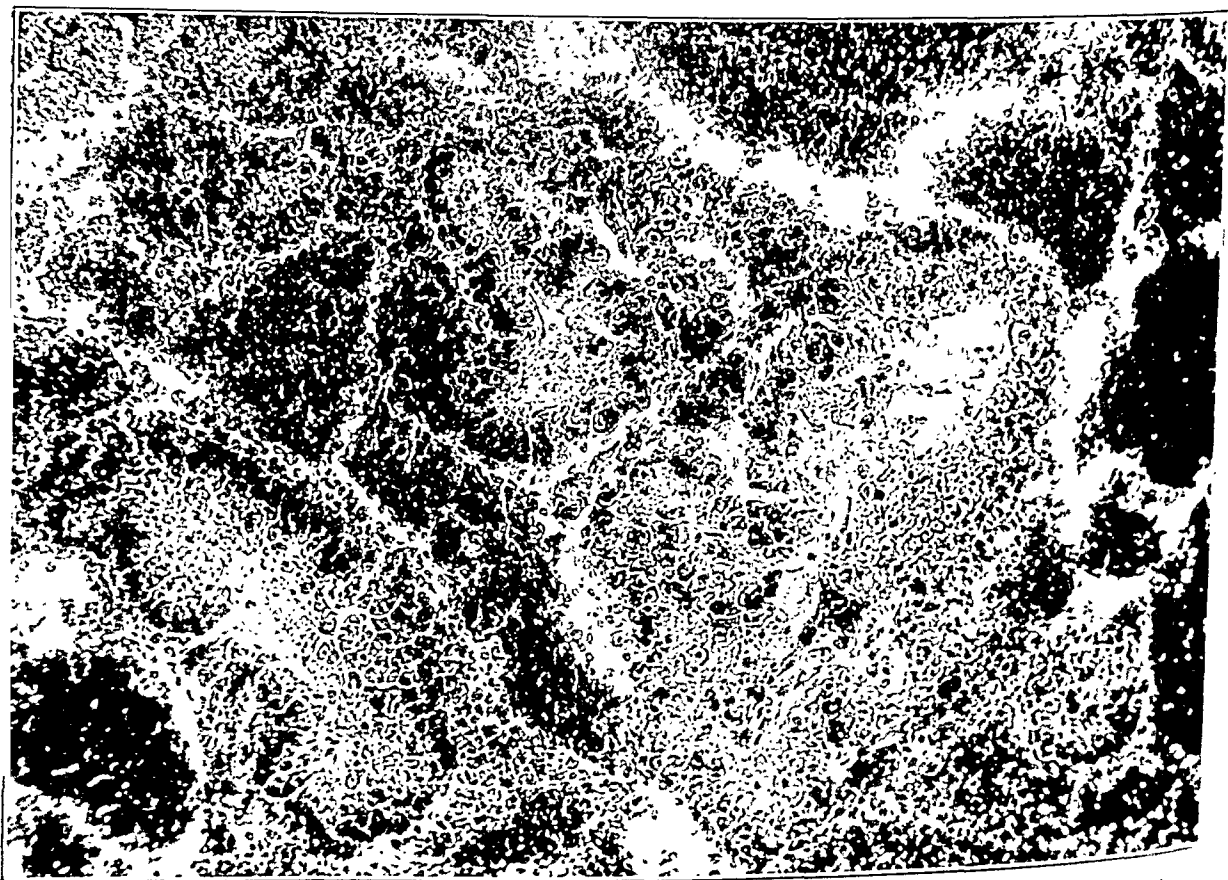


Fig. 15 (case 29).—Section through another portion of the same tumor as in figure 14, showing the papillary carcinomatous appearance. Reduced from a magnification of $\times 240$.

In some areas the cells formed pseudo-alveoli. There was a thin capsule surrounding the tumor. The adjacent kidney tissue was compressed. This tumor gave the impression of a relatively benign growth.

CASE 31.—G. R., a man, aged 67, died of generalized arteriosclerosis, hypertrophy of the prostate and bilateral hydronephrosis. A small tumor was found in the right kidney. On section, there were several irregular masses of cells surrounded in part by a connective tissue capsule and compressing the surrounding kidney tissue. The cells were arranged in solid plates and cords, forming in places pseudo-alveolar structures. There were large cystlike spaces, areas of hemorrhage and cavernous spaces filled with blood. The cells were polyhedral and round, and the cytoplasm was pale-staining. The nuclei were small, deeply chromatic and eccentric. In places the cells were arranged in columns, separated by finely dilated capillaries. In other areas, the cells showed a loss of definite arrangement, growing widely in a loose stroma. They showed a moderate degree of pleomorphism. This was a malignant hypernephroma.

CASE 32.—L. F., a woman, aged 52, died following a laminectomy for a suspected cord tumor. In the left kidney, there was a small tumor, 4 cm. in diameter; it was sharply defined, with a fine capsule. The tumor consisted of polyhedral cells arranged in columns separated by fine connective tissue septums containing capillaries. In some places, the appearance was that of typical suprarenal cortical tissue. In other areas, the cells were more irregular and closely packed and contained less lipid material. In these areas there were hemorrhage, necrosis and degeneration. This was a typical hypernephroma.

CASE 33.—F. R., a man, aged 67, died of carcinoma of the colon. A small tumor of the left kidney was found at autopsy.

On section, in many areas the appearance was that of a typical hypernephroma. There were other areas, however, where the cells were irregular with closely packed nuclei, showing marked pleomorphism. Hemorrhages were present. This was a malignant hypernephroma.

CASE 34.—S. G., a woman, aged 64, died of hypertension and diabetes. A small tumor was found in the right kidney.

The nodule consisted of pyramidal cells arranged in large sheets with a fine connective tissue stroma containing capillaries. The cells were foamy and contained small eccentric nuclei. In the central portion of the nodule there were numerous cystlike spaces. There was no sharply defined capsule. The cells invaded the medulla of the kidney. The walls of the several veins were invaded by hypernephroma cells.

This was a typical hypernephroma. Though invasion of the walls of the veins is found occasionally in benign adenomas of the suprarenal cortex, this may be an indication of a malignant condition (fig. 16).

CASE 35.—M. H., a man, aged 64, died of arteriosclerotic heart disease. There was a tumor in the left kidney, 3 by 4 cm. It was composed of a highly cellular tissue, in places forming pseudo-alveoli. Very little connective tissue stroma was present. The tumor cells were irregular, round and polyhedral. They did not contain a large amount of lipid material. Many of the nuclei showed a moderate degree of variation. There were areas of hemorrhage.

Grossly, the tumor was yellowish and resembled suprarenal cortical tissue. Although it was not a typical hypernephroma, the gross appearance and some of its histologic characters warrant its inclusion in this group. The tumor may be an adenoma with fatty cells.

CASE 36.—J. R., a man, aged 78, died of hypertension and arteriosclerotic heart disease. There was a tumor 2.5 cm. in diameter in the left kidney.

On section in some areas, the structure was of a typical hypernephroma with the regular arrangement of polyhedral cells and fine capillaries. In other places, there were definite papillary structures and pseudo-alveolar formation.

CASE 37.—M. G., a man, aged 23, died of diabetes, cystitis and pyelonephritis. There was a small tumor in the right kidney.

In the wall of a large abscess of the kidney there was found a group of cells having the typical appearance and arrangement of hypernephromatous cells. The

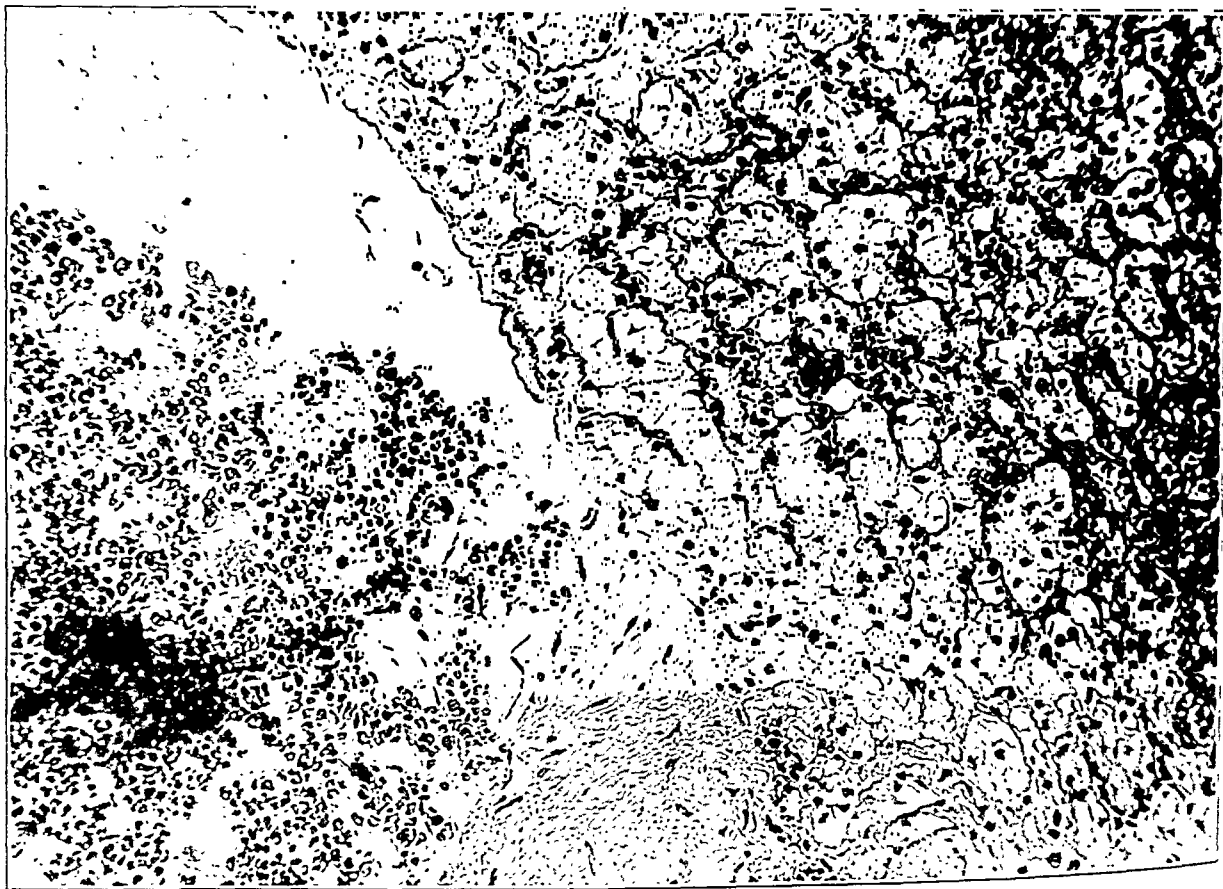


Fig. 16 (case 34).—Section through the wall of a venous space, showing invasion of the wall with hypernephroma cells. Reduced from a magnification of $\times 240$.

extensive amount of necrosis and destruction due to secondary infection prevented more detailed study of the tumor. This was a typical hypernephroma with secondary infection.

CASE 38.—J. T., a man, aged 65, died of fibroid phthisis. A tumor 2 cm. in diameter was found in the left kidney.

Section consisted of a nodule of cells surrounded by a thin capsule of connective tissue. The surrounding kidney tissue was compressed. The nodule was composed of large numbers of polyhedral cells arranged in a mosaic and in columns separated by fine capillary connective tissue. The cytoplasm in the cells was vacuolated and foamy. The nuclei were eccentric and small, but showed some

degree of variation in size. In places a definite formation of lumina was seen, and the cells had an alveolar arrangement. In other places, cystic areas with hemorrhage were present. Hemosiderin pigment in large amounts lay in and between the cells. This was a typical malignant hypernephroma.

CASE 39.—I. L., a man, aged 62, died of arteriosclerotic heart disease and hypertension. At autopsy, a small Grawitz tumor was found in the left suprarenal gland.

A typical hypernephroma with large sheets of foamy pyramidal cells possessing eccentrically placed nuclei and a fine supporting connective tissue stroma were seen. In the central portion of the tumor, there were several large cystlike spaces filled

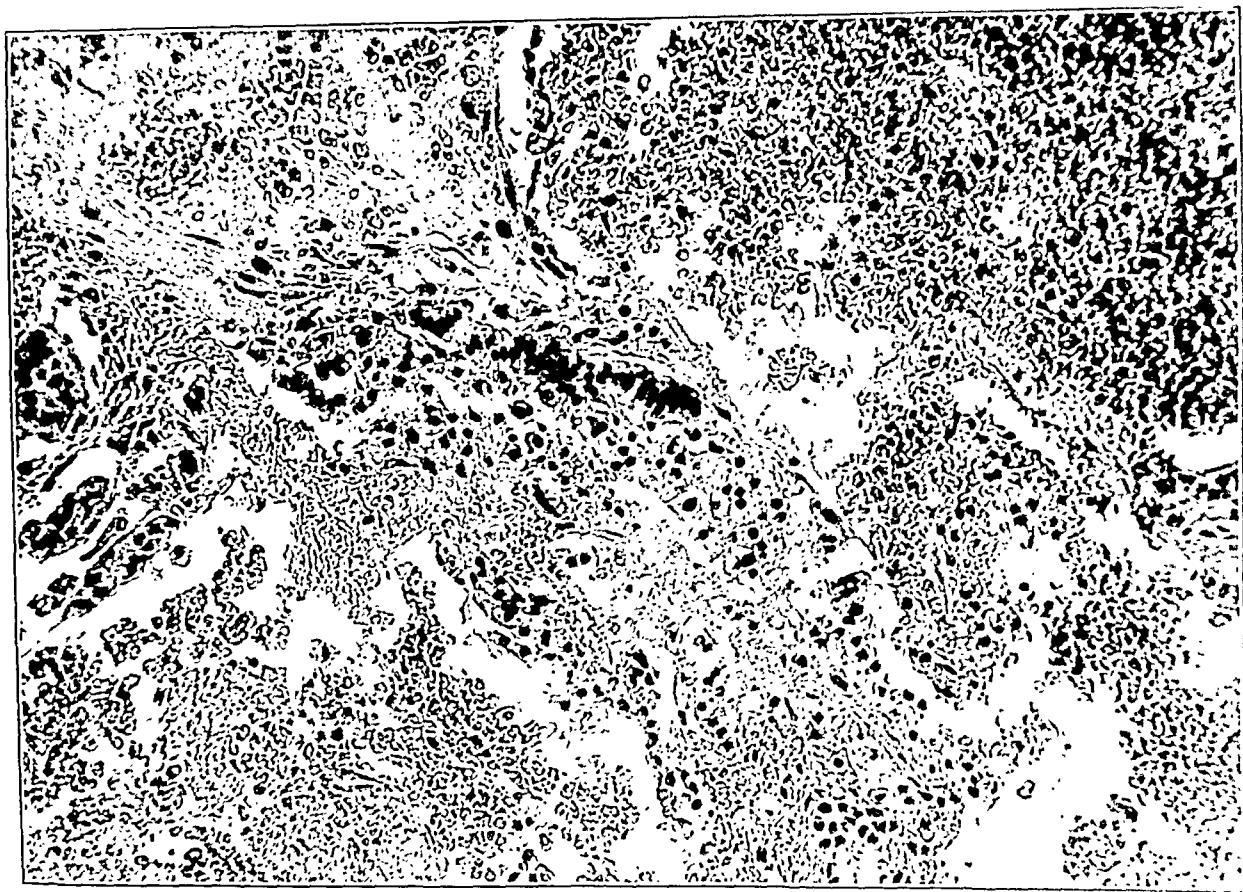


Fig. 17 (case 39).—Section showing the transition of the character of the tumor cells from typical foamy hypernephroma cells to the cuboidal "epithelial" cells lining cystlike spaces. The increase in chromatin content of the nuclei is clearly seen. Reduced from a magnification of $\times 240$.

with blood and serum. There were gradations from islands of hypernephroma cells in clumps to isolated small islands lying in a homogeneously staining stroma. Here the honeycombed character of the cells was lost, the cytoplasm became pink-staining, and the cells became cuboidal and cylindric, losing their polyhedral character. The tumor that was definitely of suprarenal origin showed some of the glandlike appearance commonly observed in hypernephroma of the kidney.

This was an adenoma of the suprarenal gland, showing early changes of malignancy with the development of papillary structure (figs. 17 and 18).

CASE 40.—L. F., a man, aged 37, died of multiple sclerosis. A tumor, 9 cm. in diameter, was found in the left kidney.

Section consisted of large numbers of polyhedral cells arranged in a mosaic, and in places in irregular alveolar formation. The stroma was extremely scant and formed a fine network containing numerous distended capillaries. In some areas the cells appeared in small clumps, particularly, and at the periphery of the nodule they lay free in a loose stroma. The cells were large and vesiculated; the nuclei were eccentric and varied in size and chromatin content. In some areas they were larger and contained two nuclei. The cells in general were somewhat larger than those in the typical hypernephroma. This was a malignant hypernephroma.

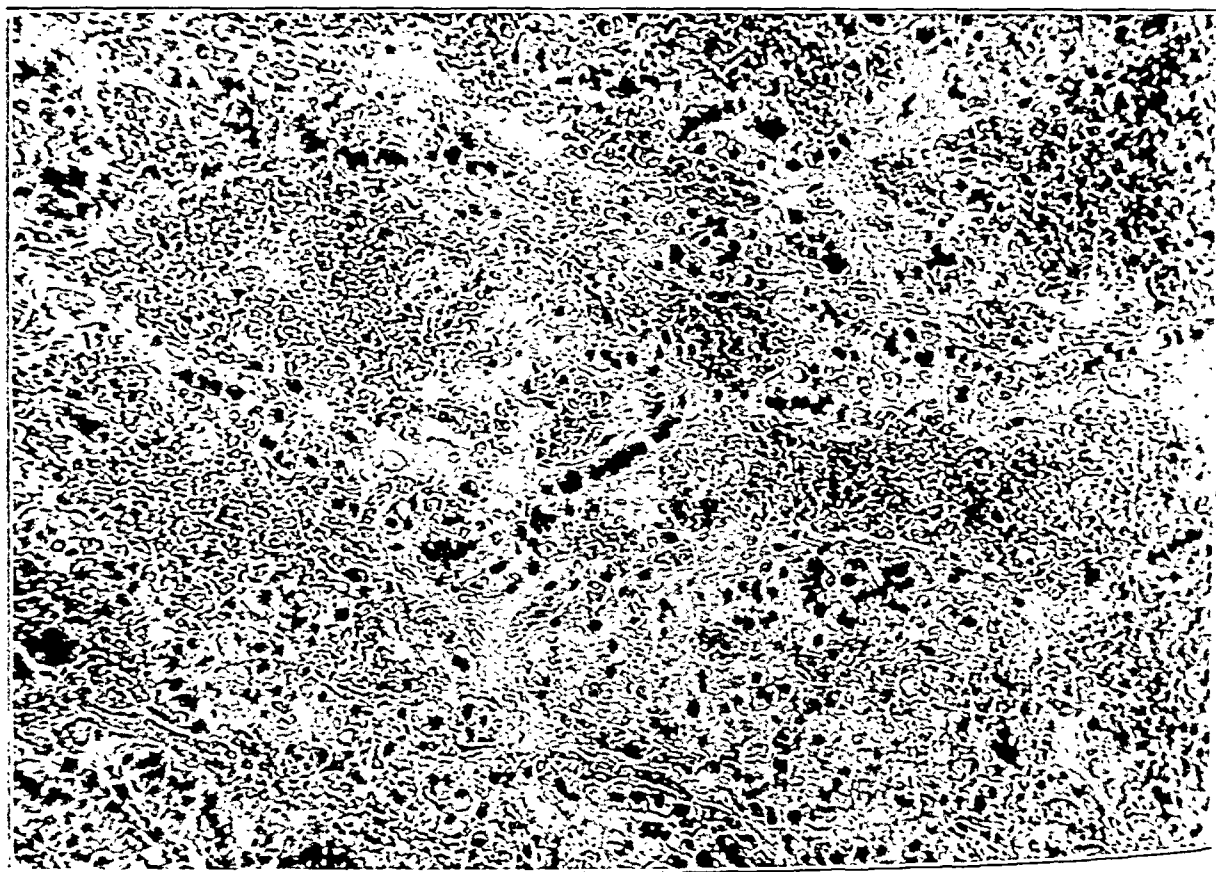


Fig. 18 (case 39).—Section showing large cystlike spaces filled with blood with strips of cuboidal cells such as are seen in figure 4. Reduced from a magnification of $\times 240$.

CASE 41.—R. S., a woman, aged 61, died of endothelioma of the brain. The upper two thirds of the left kidney were replaced by a Grawitz tumor. Section showed a partially encapsulated nodule, compressing the adjacent kidney tissue. The capsule contained blood and pigment. The nodule consisted of solid sheets of foamy cells arranged in columns with a fine stroma of connective tissue and capillaries. Considerable pigment was present. The cytoplasm in places was clear, and in other places had a more definite honeycomb appearance. The nuclei were more or less regular in size, with slight variations. The resemblance to the fascicular layer of the suprarenal cortex in one area was extremely suggestive.

This was a hypernephroma showing the malignant transformation of a benign tumor arising from the cortical suprarenal tissue in the kidney.

CASE 42.—L. C., a man, died of generalized arteriosclerosis and hypertension. There was a tumor 7 by 5 by 5 cm. in the left kidney.

On section, the tumor was composed of masses of fairly uniform polyhedral cells arranged in a continuous mosaic. The cytoplasm was foamy; the nuclei were small and eccentric. Between every two or three columns of cells there were fine septums containing capillaries. This portion of the tumor was perfectly uniform and benign, having a resemblance to the fascicular layer of the cortex of the supra-

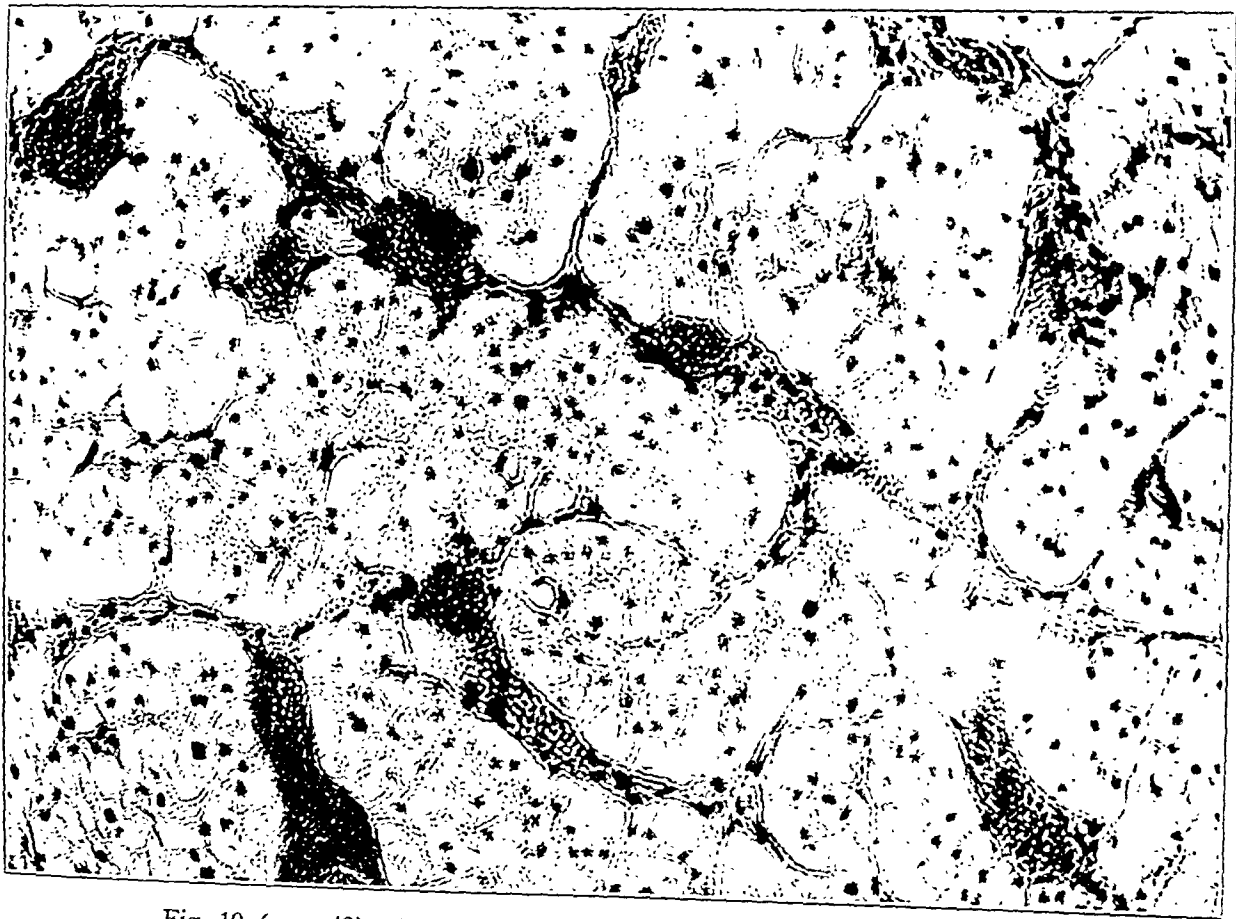


Fig. 19 (case 42).—Benign appearance of the hypernephroma cells. Note the uniformity in size of the nuclei, the honeycomb structure of the cytoplasm and the mosaic arrangement of the cells. Reduced from a magnification of $\times 240$.

renal gland. Other sections of the tumor showed the structure typical of a malignant hypernephroma with cyst formation, hemorrhage and necrosis. There was marked pleomorphism of the cells and nuclear elements, and in some areas the cells lay singly and were extremely large. Giant cells with large irregular nuclei were present.

This was a striking instance of the transition of a benign growth into a malignant one. A section from one or two areas of the tumor would have failed to reveal the striking malignant character of the growth (figs. 19 and 20).

CASE 43.—M. L., a man, aged 70, died of carcinoma of the esophagus. There was a pea-sized nodule in the left kidney.

On section, the nodule was small and encapsulated, and it compressed the surrounding tissue. It was composed of polyhedral cells arranged in irregular columns and lying in a network of thin connective tissue containing capillaries. The cytoplasm was honeycombed. In places small lumina had a pseudo-alveolar formation. In other areas, a typical hypernephroma was seen. The central portion of the nodule contained large quantities of blood, which lay in cystlike spaces. In other places, definite glandlike structures were distended with blood and were lined

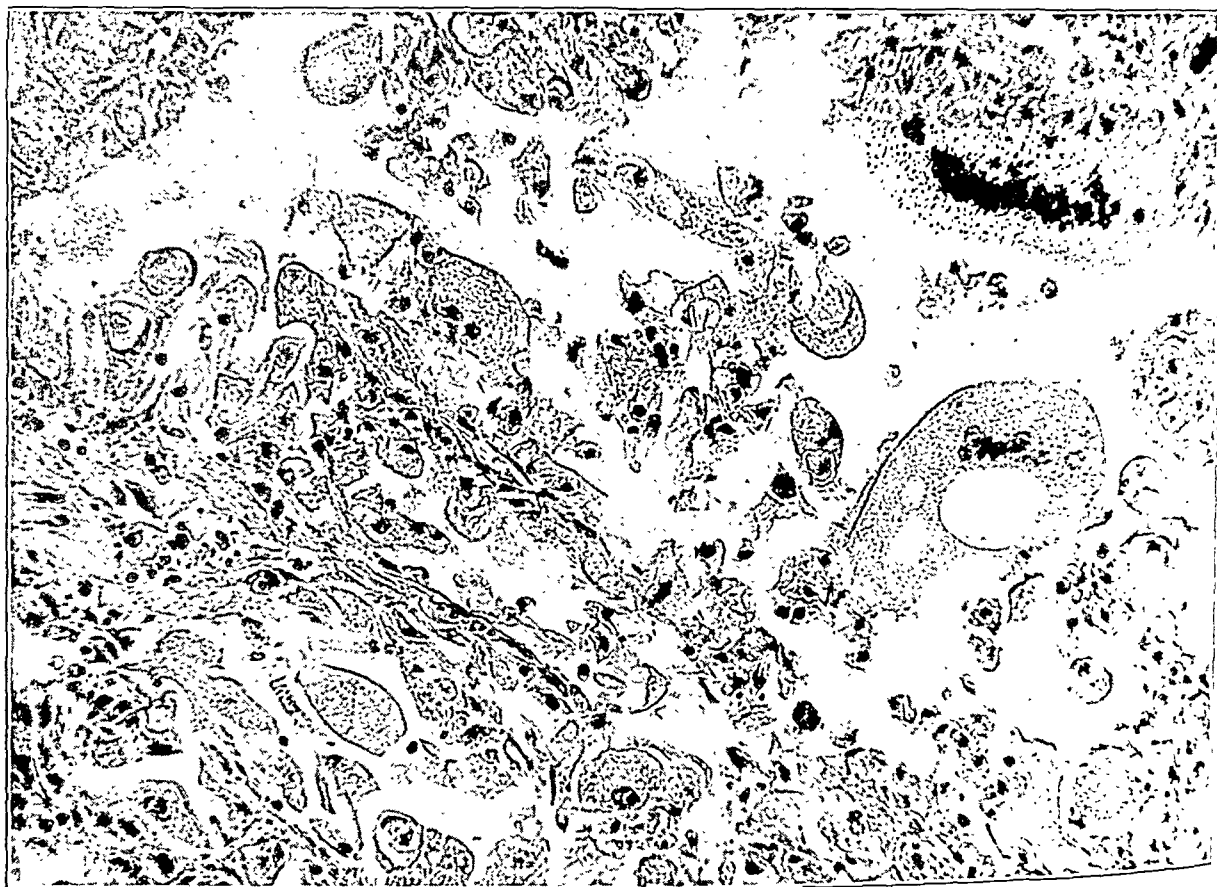


Fig. 20 (case 42).—Section showing marked pleomorphism of the tumor cells with evidence of papillary structure and giant cell formation. Reduced from a magnification of $\times 240$.

by clear, vacuolated, cuboidal, polyhedral cells. This was a typical benign hypernephroma.

CASE 44.¹⁶—M. F., a man, aged 24, died of uremia and hypertension. At autopsy, a large tumor of the suprarenal gland was found.

The tumor consisted of columns and masses of polyhedral cells closely packed and lying in an irregular stroma of connective tissue. The cells showed marked pleomorphism. There was a tendency toward alveolar formation and the develop-

16. This case was reported by Dr. B. S. Oppenheimer and Dr. A. Fishberg.

ment of papillae. In other areas, the tumor resembled the cortex of the suprarenal gland. Necrosis and hemorrhage were present. The left suprarenal gland contained ten benign adenomas.

The diagnosis was hypernephroma of the suprarenal gland arising from a benign adenoma. The relation between benign and malignant hypernephroma was strikingly illustrated.

PATHOGENIC GAS-PRODUCING ANAEROBIC BACILLI IN CHRONIC ULCERS*

MELVILLE H. MANSON, M.D.

MINNEAPOLIS

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Summary

Two virulent cases of gas gangrene following amputation of extremities that were the site of chronic ulcers stimulated interest in this subject. Gas gangrene is usually the result of severe trauma with muscle destruction and a wound grossly contaminated with dirt and foreign bodies. The problem presented itself as to the origin of the gas bacillus infection in postoperative wounds, in which all the usual aseptic and antiseptic precautions had been employed, and the possible relationship of the ulcers to the development of the gas bacillus infection was suggested. This paper includes a report of two cases and a bacteriologic study of chronic ulcerating lesions with particular reference to the occurrence of the pathogenic, gas-producing anaerobes.

REPORT OF CASES

CASE 1.—G. K., aged 43, a barber, was admitted to the University Hospital on Sept. 30, 1929. He had a history of diabetes dating back to 1917, twelve years prior to admission, for which he had taken no treatment. In August, 1929, he noted a small scab on the anterior tibial aspect of his left leg, which increased in

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size and became quite painful. Local treatment was instituted, but the ulcer increased in size and at the time of admission measured about 5 cm. in diameter. There was considerable infection present, the area surrounding the lesion being reddened, edematous and indurated. The patient was placed on a basal maintenance diet, and conservative treatment was directed to the ulcer.

Roentgen examination of the left leg showed calcified thrombi in the veins. There was a distinct destructive process in the cortex of the anterior surface of the tibia with little or no new bone formation. The appearance was characteristic of secondary invasion of the bone with a soft tissue infection that was producing considerable bone destruction. There was no evidence of gas in the soft tissues.

Amputation was advised, but the patient refused. Conservative local measures consisting of elevation of the extremity, application of packs saturated with surgical solution of chlorinated soda (Dakin's solution) and heat were continued, together with careful dietary regulation for the diabetes.

On October 25, as the ulcer had shown no evidence of improvement and was causing the patient considerable pain, he consented to amputation, qualifying his consent, however, to the extent that the amputation be done below the knee. Because of the close proximity of the ulcer to a satisfactory amputation level and the presence of the diabetes, he was advised that an amputation through the lower thigh would be a safer procedure. This opinion was not shared by the patient.

The lesion was covered with sterile dressings, the leg prepared by cleansing with benzine and ether, application of two coats of 3.5 per cent alcoholic iodine solution which, after drying, was removed with Richardson's¹ solution. Under spinal anesthesia, the leg was amputated about 5 cm. below the tibial tubercle. A tourniquet was used on the thigh and was left on for not more than five minutes. Bleeding was apparently free on its removal; the muscles appeared normal, and the flaps were closed over a split Penrose drain.

The immediate postoperative course was very satisfactory. The stump was dressed the following day and appeared in healthy condition. On the evening of the third day, the patient complained of considerable pain in the stump. His temperature was elevated to 102.6 from 99 F. The dressings were removed, and the characteristic odor of gas gangrene was immediately noted. There were several copper-colored blebs present; the edges of the flaps were of a gunmetal blue and gas was palpable, especially on the medial aspect to the junction of the lower and middle thirds of the thigh. Roentgen examination showed a large amount of gas in the soft tissues about the stump, extending well up along the shaft of the femur to about 10 cm. above the knee joint (fig. 1).

Under spinal anesthesia, a quick amputation through the upper thigh was done by the transfixion method. All of the muscles except the gracilis appeared normal in color, reacted to stimulation and bled freely. The gracilis was dissected upward until it was no longer brownish and contracted when stimulated. The flaps were not closed. Prior to the operation, 20 cc. of *Bacillus perfringens* antitoxin was given intramuscularly; 150 cc. was injected into the stump at the time of the operation.

The patient's condition was critical the next morning, and 20 cc. of *Bacillus perfringens* antitoxin was given intravenously, together with physiologic solution

1. This is the routine skin preparation at the University Hospital. Sodium thiosulphate neutralizes the iodine and removes the iodine stain much more efficiently than does alcohol alone. This technic was introduced nine years ago by Dr. Fred Richardson, of Minneapolis, then an intern at the hospital.

of sodium chloride. There was considerable abdominal distention; the blood sugar, which had been 150 mg., rose to 600 mg. The pulse became rapid and thready about noon the day following operation, and death occurred.

Postmortem examination showed the amputation stump to be clean. There was no discoloration, no odor and no crepitation. The subcutaneous fat was about 10 cm. in thickness, and there was an enormous amount of fat in the peritoneal cavity. There was a marked sclerosis of the coronary arteries, especially the left branch. The lumen was pinpoint in size, and in the same region myocardial

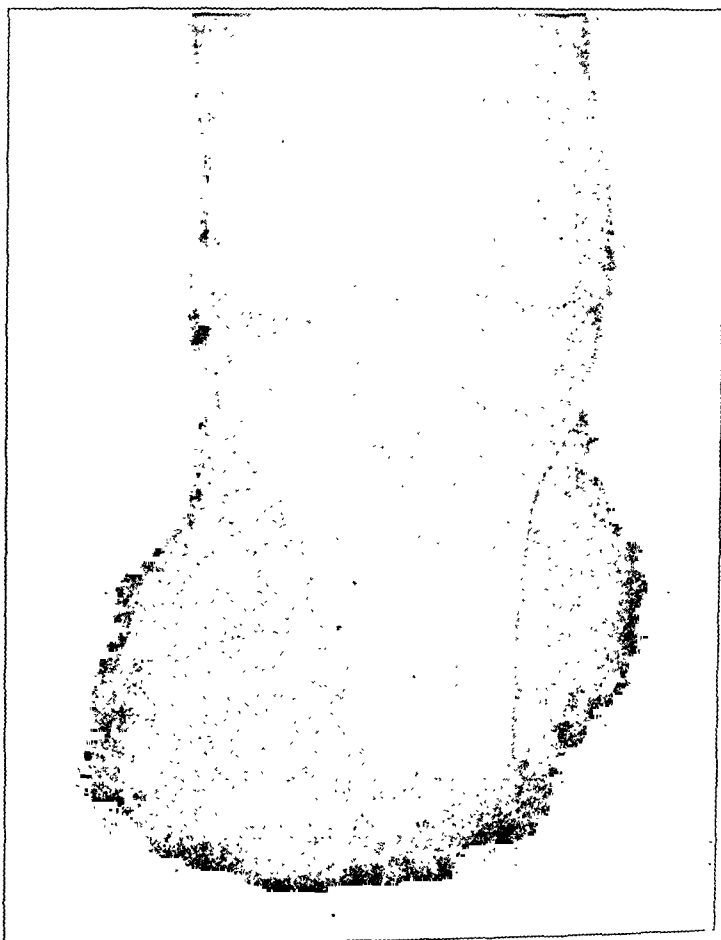


Fig. 1 (case 1).—Roentgenogram taken immediately prior to secondary amputation. Diffuse mottling of soft tissues with gas extending upward on lateral sides above knee joint is shown.

fibrosis was seen. No gas was found in the blood vessels or in the liver. There were a chronic cholecystitis and cholelithiasis, cloudy swelling of the kidney and liver and a healed miliary tuberculosis of the pleura, spleen, kidney and liver.

CASE 2.—H. W., a man, aged 55, was admitted to the hospital on Sept. 17, 1929, and died on Feb. 18, 1930. He was undernourished and prematurely senile, and entered the hospital with a chief complaint of an ulcer on the left heel. The immediate history preceding the onset of the ulcer was that in December, 1928, the patient experienced what he termed chilblains of both feet, more marked

on the left than on the right. The left heel cracked at the site of a callus, and a sore developed underneath, which was opened. In August, 1929, the lesion was excised and curetted down to the bone, following which healing did not occur. The patient's history showed that he had had syphilis, the onset of which was twenty years prior to admission. He had had several courses of treatment, the last ending in August, 1929.

Examination showed a deep, indurated ulcer on the left heel, from which exuded considerable purulent discharge. Treatment consisted of irrigations with

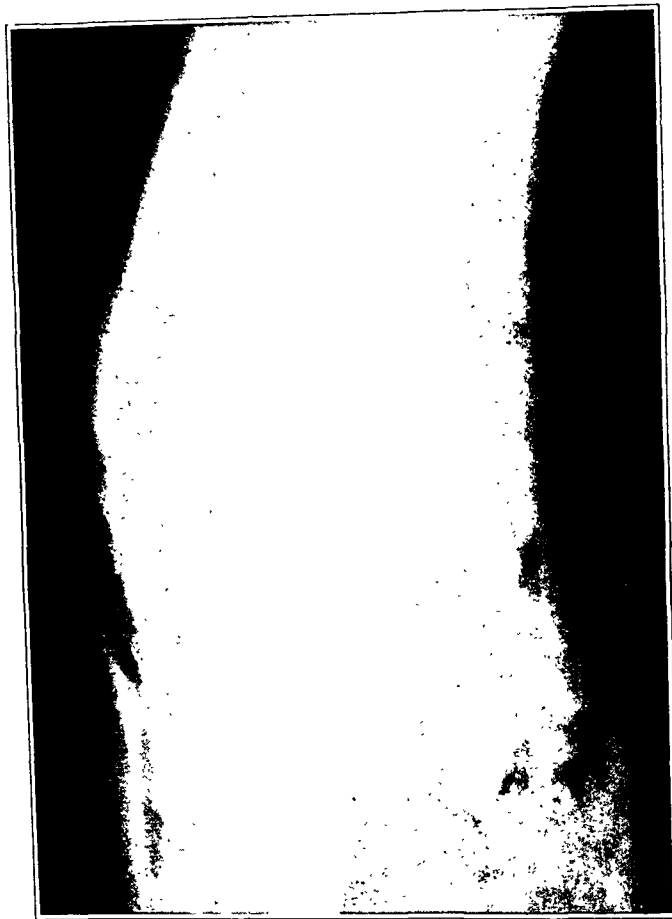


Fig. 2 (case 2).—Roentgenogram taken immediately prior to secondary amputation. Bubbles of gas are seen throughout the soft tissues extending upward along the femur.

surgical solution of chlorinated soda, elevation and heat. There was no response to conservative treatment, and on October 11 the ulcer was excised, following which the wound was treated with packs saturated in surgical solution of chlorinated soda. By November 4, the granulations appeared quite healthy, and the transfer of a pedicle flap from the calf of the right leg was contemplated. This flap was outlined and raised and resutured to its bed preparatory to a transfer. The lower portion of the ulcer was excised. The exposed bone was removed with a chisel and the curet, leaving a free bleeding raw surface. The ulcer, however, failed to granulate, and this plan was abandoned. Further antisyphilitic treatment

was instituted. During this course of treatment, the patient complained considerably of severe pain in the foot, was unable to sleep at night and required considerable narcotics for relief. Circulatory tests of the lower extremity showed an oscillometric index with the Paschon oscillometer of a half above the right ankle, zero above the left ankle, one and one-half above the left knee and from six to seven oscillations above the right knee.

The pain that the patient was experiencing was attributed to the circulatory inadequacy, and because of the extreme pain and the election on the part of the patient, an amputation was done on January 23 under spinal anesthesia, the left leg being amputated about 8 cm. below the tibial tuberosity. Preparation of the skin was the same as in the preceding case. On the morning of the third postoperative day, a definite odor of gangrene was noted about the stump, and on examination there were several discolored brownish blebs. The distal end of the stump appeared rather purplish, and on palpation definite crepitation could be felt, most marked on the medial aspect of the thigh as high as about the middle of the stump. *Clostridium welchii* was identified in the exudate (fig. 2).

On January 25, an amputation through the middle thigh was done under spinal anesthesia. Prior to amputation, 30 cc. of *Bacillus perfringens* antitoxin was given intravenously and 150 cc. injected into the stump. The stump was left open, and subsequent treatment consisted of irrigations with surgical solution of chlorinated soda. Later, the same day, 100 cc. of *Bacillus perfringens* antitoxin was given intramuscularly; on January 29, 20 cc. was given intramuscularly.

The postoperative course was uneventful until the ninth day, when a rather severe secondary hemorrhage occurred. The entire stump was opened, the hemorrhage controlled, and the patient given a transfusion with 600 cc. of whole blood. No further evidence of gas gangrene manifested itself. The patient's subsequent course, however, was complicated by the fact that he had urethral strictures, which, following the postoperative catheterization, totally obstructed the urethra. A ureteral catheter was used for drainage, and infection developed. A suprapubic cystotomy was done. Subsequently, bronchopneumonia developed, and the patient died on Feb. 18, 1930.

Postmortem examination showed no evidence of gas gangrene. There was bilateral bronchopneumonia and marked infection of the entire urinary tract.

Summary of Cases.—The case histories of two patients presenting chronic ulcers necessitating surgical intervention because of their resistance to conservative treatment are reviewed. In one patient, who had diabetes, the ulcer and the concomitant infection had a reciprocal deleterious influence on the diabetes. The other patient had syphilis and suffered from a painful ulcer on the heel. Amputation of the ulcer-bearing extremity below the knee was done in both instances. The disability from pain was great in both cases. On the third postoperative day, gas gangrene developed in the amputation stumps. There was no evidence of, or reason to suspect, gas bacillus infection in the ulcers prior to operation.

SUGGESTED RELATIONSHIP BETWEEN CHRONIC ULCERS AND GAS GANGRENE

Because of the similarity of the two cases and the fact that no other cases of gas bacillus infection developed in patients who were operated

on at the same time, it appeared likely that the source of the infection may have been the chronic ulcers. No reference has been found in the literature regarding the development of gas gangrene in a chronic ulcer, although several cases of tetanus in which an ulcer was the portal of entry have been reported (Andrews and Horder,² Schmüziger,³ DaCosta⁴). The possibility of contamination from the skin or from the catgut employed is unlikely. This will be discussed more fully under comment. The logical premise to determine this suggested relationship would be the frequency with which chronic ulcers harbor pathogenic anaerobes. Consequently, cultures were made of this type of lesion from patients being treated in the dispensaries or wards of the University Hospital.

TECHNIC

Isolation of Anaerobes.—Material to be cultured was obtained on a sterile applicator and placed in a sterile glass test tube. The swab was then transferred to liver peptone or dextrose brain-broth medium. This had been boiled for fifteen or twenty minutes and cooled immediately prior to its use. After incubation for from twenty-four to forty-eight hours, the culture was usually examined for the presence or absence of spores. If spores were present, the culture was heated to 80 C. for fifteen or twenty minutes to kill the nonspore-forming rods and cocci that were usually present. The culture was then plated anaerobically on Adams'⁵ dextrose sodium sulphite, ferric chloride agar and incubated for twenty-four or forty-eight hours. This medium was freshly made before each plating by adding to a tube of dextrose agar 1 cc. of sodium sulphite solution (20 Gm. anhydrous salt to 100 cc. of water) and 0.1 cc. of ferric chloride solution.

Anaerobic growth is indicated on this medium by the appearance of typical black colonies. Single colonies were picked and planted into deep shake-agar tubes, milk and liver peptone, or brain-broth medium. The brain-broth was used exclusively in the latter part of this study. The stormy fermentation in milk, produced by a gram-positive, nonmotile anaerobic bacillus, was considered characteristic of *Clostridium welchii*. It was found later that purification was rendered somewhat easier by utilizing the fact that *Clostridium welchii* reproduces at a much earlier period than most other organisms. That is, in a favorable medium containing fermentable sugar, as the dextrose brain medium, *Clostridium welchii* will attain vigorous gas production in three or four hours, while staphylococci, streptococci and the gram-negative rods will either not be in evidence, or be in an exceeding minority. Thus,

2. Andrewes, F. W., and Horder, T. J.: A Case of Tetanus: Isolation of the Bacilli from a Varicose Ulcer; Treatment by Antitoxin; Recovery, *Lancet* **1**:685, 1917.

3. Schmüziger, P.: Ein Fall von Tetanus mti Ulcus curis als Eingangspfort, *Deutsche Ztschr. f. Chir.* **188**:161, 1924.

4. DaCosta, J. C.: *Modern Surgery*, ed. 10, Philadelphia, W. B. Saunders, 1931, p. 136.

5. Adams, B. A.: The Enumeration of the Anaerobic Sulphite Reducing Bacteria and the Significance of Their Presence in Water, *Water and Water Engineering*, Sept. 20, 1929.

by transferring the culture into fresh medium every three or four hours, the Welch bacillus may be isolated from the less rapidly reproducing organisms in the course of about two days.

Pathogenicity.—Inoculation of from 0.5 to 1 cc. of a twenty-four hour culture in guinea-pigs was made in every case in which a gram-positive anaerobe was isolated. The hair was clipped, the skin prepared with tincture of iodine and the culture injected intramuscularly into the thigh. A typical reaction in a guinea-pig consists of an edema which progresses rapidly, with gas formation that is palpable within two or three hours. The skin may exude serum or may slough, and death occurs in from eight to twenty-four hours if the culture is virulent. In some cases a spontaneous perforation occurred, in which event recovery not infrequently ensued (figs. 3 and 4).



Fig. 3.—Guinea-pig two weeks after inoculation of culture from case 7 into the right thigh. The large gangrenous area later sloughed off and healing resulted.

Differentiation of Organisms.—Gram-positive anaerobes, other than *Clostridium welchii*, were differentiated by the most prominent cultural and morphologic characteristics in which they differ from the Welch bacillus. Differentiation between *Clostridium edematis-maligni* (vibrion septique) and *Clostridium welchii* was based on the fact that the former is somewhat more slender and is motile, whereas the latter is short, stubby and nonmotile. Cultures of *edematis-maligni* in milk produce acid and clotting. This occurs at a later period and is distinctly a different reaction from the stormy gas fermentation that is evoked by the Welch bacillus.

Sporogenes is also a motile organism, and is easily differentiated from *Clostridium welchii* in that it is strongly proteolytic, and the reaction resulting from its activity is alkaline rather than acid. The proteolysis is recognized by the

blackening of the brain* in a broth culture, due to the formation of sulphides. A putrid odor results from this action which is very offensive.

Bacillus subtilis, *megatherium* and related organisms are morphologically very similar to *Clostridium welchii* but are easily differentiated by their profuse aerobic growth characteristics.

Technic for Clinical Application.—It is apparent that the technic as described is too lengthy and detailed to be of value if one wishes only to determine whether or not the Welch bacillus is present in any lesion. Any "short cut" method in bacteriology is apt to result in unreliable results and, in general, is not to be encouraged. However, the milk reaction to the growth of *Clostridium welchii* is a phenomenon sufficiently characteristic to warrant its use as a diagnostic procedure. This stormy fermentation has been used as a criterion for the presence of *Bacillus welchii* by Glynn,⁶ Hewes and Kendall,⁷ Orton,⁸ Rettger,⁹ Simonds¹⁰ and others.



Fig. 4.—Same guinea-pig as shown in figure 3. The perforation is seen leading to a necrotic cavity which previously contained gas and sanguineous fluid. The perforation occurred about thirty hours after the injection of the culture.

The method consists simply of boiling a tube of fresh milk—whole milk is preferable—for from twenty to thirty minutes immediately prior to its use. This is

6. Glynn, E. E.: The Relation Between *Bacillus Enteritidis* Sporogenes of Klein and Diarrhea, Thompson Yates Lab. Rep. **3**:131, 1900-1901.

7. Hewes, H. F., and Kendall, A. I.: The Gas Bacillus as an Agent of Intestinal Fermentation and Diarrhea, Boston M. & S. J. **166**:75, 1912.

8. Orton, S. T.: A Note on the Occurrence of *B. Aerogenes* Capsulatus in an Epidemic of Dysentery and in the Normal, J. M. Research **29**:287, 1913-1914.

9. Rettger, L. F.: Studies on Putrefaction, J. Biol. Chem. **2**:71, 1906.

10. Simonds, J. P.: Studies in *B. Welchii* with Special Reference to Classification and to Its Relation to Diarrhea, New York, Rockefeller Institute for Medical Research, 1915, no. 5.

cooled rapidly. A swab from the suspected lesion is introduced, and the culture placed in an incubator at 37.5 C. If the Welch bacillus is present, gas bubbles may be seen rising to the surface within two or three hours, and within a period of six or eight hours the whole content will be involved by the rigorous gas production. At the end of twenty-four hours the milk is separated into a clean whey, and the clot is torn and fragmented throughout the tube.

The question may arise as to the least number of spores or organisms necessary to produce this reaction, for if it is not selective enough, some lesions containing only a few organisms might be considered negative. Simonds¹⁰ found that dilutions that yielded two or three colonies when planted on anaerobic agar plates invariably gave positive reactions in milk. In most instances in which there was but one colony on a plate, there was a positive milk reaction. Thus it is seen that the method is sufficiently selective to be of definite value, and because of its simplicity should be used more extensively.

RESULTS

Culture of thirty-two chronic ulcerating lesions revealed that eleven, or 34.37 per cent, were harboring pathogenic, gas-producing anaerobes. *Clostridium welchii* was present in each of the eleven positive cultures, associated with *Clostridium edematis-maligni* (vibrion septique) in two instances. *Clostridium tetani* was isolated in one case. In two instances (cases 7 and 10), the Welch bacillus was isolated on repeated occasions. The cultures of sporogenes were not pathogenic for guinea-pigs. The organisms designated in the table as facultative will be discussed in more detail in the control series. Only the bacilli that were pathogenic for guinea-pigs are controlled *Clostridium welchii* in this series. The table on the next page indicates the type of lesions cultured.

Analysis of the results with regard to sex or age shows no significant findings. The duration of the varicose ulcers from which the anaerobes were isolated averaged approximately six years longer than that of the ones that yielded no anaerobes. This does not include the case of forty-five years' duration. Whether the longer duration was due to the presence of the anaerobes is difficult to determine. The appearance of the ulcers that contained the anaerobes was of no apparent significance, and none of them developed any evidence of gas bacillus infection. The environment of the patients as determined by their occupation was not analyzed in detail. It has been suggested that those who are in closer contact with the soil, as farmers, might harbor this group of organisms more often than people employed in other occupations. The patient from whom *Clostridium tetani* and *Clostridium welchii* were obtained was a farmer (case 3). Case 21, from which *Clostridium edematis-maligni* and *Clostridium welchii* were both isolated, was also that of a farmer. None of the other patients were employed in the country at the time the positive cultures were obtained.

Types of Lesions Cultured *

Patient	Sex	Age	Lesion	Duration	Culture
1. A. J.	F	27	Ulcer at site of toe amputation....	2 yrs.	No anaerobic growth
2. M. L.	M	76	Ulcer at site of thigh amputation..	6 yrs.	No anaerobic growth
3. C. M.	M	47	Trophic ulcer of heel.....	2 yrs.	Clostridium tetani and Clostridium welchii
4. W. B.	M	31	Varicose ulcer, left leg.....	8 yrs.	Clostridium welchii
5. L. C.	F	38	Varicose ulcer, right leg.....	2 yrs.	No anaerobic growth
6. C. L.	F	68	Varicose ulcer, left leg.....	4-5 yrs.	No anaerobic growth
7. A. H.	F	66	Varicose ulcer, left leg.....	16 yrs.	Clostridium welchii
8. W. C.	M	38	Varicose ulcer, left leg.....	2 yrs.	No anaerobic growth
9. L. F.	M	59	Epithelioma, hand	?	No anaerobic growth
10. T. S.	M	60	Varicose ulcer, left leg.....	10-15 yrs.	No anaerobic growth
			Varicose ulcer, right leg.....	4-5 yrs.	Clostridium welchii
11. E. J.	F	60	Varicose ulcer, left leg.....	?	No anaerobic growth
12. M. Y.	G	20	Ulcer following trauma.....	1 mo.	Facultative anaerobic growth
13. J. M.	M	47	Ulcer following vein injection.....	14 days	Facultative anaerobic growth
14. J. G.	M	54	Varicose ulcer	12 yrs.	Clostridium welchii
15. A. S.	F	46	Varicose ulcer, right leg.....	3 yrs.	No anaerobic growth
16. I. C.	F	34	Varicose ulcer, right leg.....	1-2 yrs.	No anaerobic growth
17. G. E.	F	22	Ulcerating erythema induratum....	6 mos.	Sporogenes and Clos- tridium welchii
18. J. E.	M	55	Sacral decubitus ulcers.....	10 days	Sporogenes
19. M. S.	F	64	Sacral decubitus ulcers.....	14 days	Clostridium welchii and Clostridium edematis maligni
20. C. M.	M	26	Sacral decubitus ulcers.....	10 days	Sporogenes
21. V. W.	M	51	Chronic ulcer, heel.....	5 yrs.	Clostridium welchii and Clostridium edematis maligni
22. E. E.	M	25	Ulcer, dorsum of hand.....	6 mos.	No anaerobic growth
23. W. H.	M	60	Varicose ulcer	45 yrs.	Clostridium welchii
24. J. S.	F	52	Varicose ulcer, right leg.....	7 yrs.	Facultative anaerobic growth
25. G. N.	M	61	Syphilitic ulcer, right leg.....	5 yrs.	Facultative anaerobic growth
26. F. T.	M	12	Trophic ulcer, foot; spina bifida...	6 yrs.	Facultative anaerobic growth
27. O. K.	M	47	Ulcer over left tibia; osteomyelitis.	6½ yrs.	Facultative anaerobic growth
28. B. K.	F	54	Sacral decubitus ulcer.....	Clostridium welchii
29. J. N.	F	27	Varicose ulcer, right leg.....	7 mos.	No anaerobic growth
30. P. B.	M	60	Ulcerating carcinoma of back.....	12 yrs.	No anaerobic growth
31. J. P.	F	38	Sacral decubitus ulcers.....	Clostridium welchii
32. I. E.	F	52	Varicose ulcer, right leg; purulent discharge	4-5 yrs.	No anaerobic growth

Summary

	Total	Harboring Anaerobes
Varicose ulcers	14	5
Decubitus ulcers	5	3
Miscellaneous ulcers	13	3

	Years
Average age of patients from whom anaerobic cultures were obtained.....	50
Average age of patients from whom no anaerobic cultures were obtained.....	43
Average duration of varicose ulcers harboring anaerobes	17+
Average duration of varicose ulcers minus the case of forty-five years' duration...	10+
Average duration of varicose ulcers harboring no anaerobes.....	4+

	Males	Females
Whole group	17	15
Positive culture group.....	6	5

* All of the lesions showed a variable flora of aerobic bacteria including staphylococci, streptococci, B. coli, gram-positive diplococci and gram-positive and gram-negative bacilli.

Cases Harboring Anaerobes.—CASE 3.—C. M., a farmer, aged 47, presented a deep penetrating ulcer of the left heel. The lesion was traumatic in origin due to anesthesia of the heel following a sural nerve injury. Cultures taken in June showed *Clostridium tetani*, producing typical tetanus in a guinea-pig. Cultures taken in September, in an effort to recover tetanus again, revealed *Clostridium welchii*. The patient has not shown symptoms of infection with either organism at any time (fig. 6).

CASE 4.—W. B., a man, aged 31, presented a large varicose ulcer on the medial aspect of the left leg which had been present for eight years. No surgical treatment was instituted. Cultures were positive for *Clostridium welchii*.



Fig. 5 (case 7).—Ulcer that repeatedly yielded *Clostridium welchii*. At no time was there evidence of gas bacillus infection.

CASE 7.—A. H., a housewife, aged 66, presented a varicose ulcer of sixteen years' duration, on the anterior tibial aspect of the left leg. Injection treatment for the varicosities had been in effect for two months before any cultures were taken. Cultures repeatedly showed *Clostridium welchii*. On one occasion a high degree of virulence for guinea-pigs was shown. A lethal outcome occurred in from six to eight hours after intramuscular injection. Two weeks later, the virulence was apparently attenuated. The guinea-pig lesion perforated spontaneously, and recovery ensued (fig. 5).

CASE 10.—T. S., a man, aged 60, is being treated in the outpatient department for bilateral varicose ulcers of the legs. Cultures from the ulcers on the right leg have shown *Bacillus welchii* on repeated occasions for a period of two months. No positive cultures were obtained from a large ulcer on the left leg. This may indicate that the positive cultures from the ulcer on the right leg are more than a casual finding, i. e., some factors may be present in this ulcer that are not present in the other lesion, permitting the harboring of the anaerobes.

CASE 14.—J. G., a man, aged 54, had been seen at intervals for over five years, during which time he received injection treatments for varicose veins. On the medial aspect of the lower part of the left leg there was an ulcer of twelve years' duration. The surrounding skin was marked by discoloration and suffered nutritional changes. The Welch bacillus obtained in this case killed a guinea-pig in ten hours.



Fig. 6 (case 3).—This lesion was of two years' duration. Cultures on one occasion showed *Clostridium tetani*. Three months later *Clostridium welchii* was recovered from the ulcer. No evidence of either tetanus or gas bacillus infection developed.

CASE 17.—G. E., a woman, aged 22, had multiple ulcerating lesions on her extremities, the etiologic factor being erythema induratum. Cultures showed *Clostridium welchii* and sporogenes. No gas gangrene was ever apparent.

CASE 19.—M. S., a woman, aged 64, had senile dementia and hemiplegia. She had a large sacral decubitus ulcer which yielded a pathogenic, gas-producing anaerobe, identified as *Clostridium welchii*, and a strain of *Clostridium edematis-maligni*.

CASE 21.—V. W., a farmer, aged 51, sustained an injury to his heel five years prior to admission, which resulted in an ulcer. The lesion had alternately been open and healed several times in the interim. Cultures showed *Clostridium*

welchii and *Clostridium edematis-maligni* (vibrio septique). This lesion was treated with surgical solution of chlorinated soda by means of packs and irrigations, subsequently excision and skin grafting were performed.

CASE 23.—W. H., a man, aged 60, had a varicose ulcer on the medial aspect of his right leg for forty-five years. There was a marked nutritional change in the surrounding tissues. Cultures showed the bacillus of Welch and streptococci. His veins were being treated by the injection method.

CASE 28.—B. K., a housewife, aged 54, was admitted to the hospital because of a fractured femur. She also had diabetes. A plaster cast was applied, and later a pressure sore developed over the sacral region. Cultures showed *Clostridium welchii* and staphylococci.

CASE 31.—J. P., a housewife, aged 38, developed a transverse myelitis in the lower thoracic segment of the spinal cord with paralysis of both lower extremities, incontinence and anesthesia. A large sacral ulcer developed from which cultures showed *Clostridium welchii* together with staphylococci and gram-negative bacilli

Control Cultures.—Cultures were made from the intact normal skin of fifty-two persons to determine whether or not the incidence of pathogenic anaerobic gas-producing bacilli was any greater in ulcerating lesions than on normal skin. Forty-six cultures were taken from the legs of patients presenting themselves to the admitting dispensary of the University Hospital. Four cultures were obtained from the legs of medical students and two from staff physicians.

Aerobic, motile gram-positive bacilli were obtained in every instance. These organisms were not completely identified, as they differed from *B. subtilis* and *B. megatherium* in minor cultural characteristics, but they undoubtedly belong to this group of bacilli. Five guinea-pigs were given intramuscular injections of cultures of these motile, aerobic spore-forming rods, and in each instance the organisms were nonpathogenic. A number of these cultures exhibited some anaerobic growth, with no gas formation, and it is this type of organisms that is designated as facultative in the table. There are ninety-three organisms of this genus classified in Bergey's¹¹ "Manual of Determinative Bacteriology," and probably many others which have not been completely identified.

Seven of the control cultures contained nonmotile bacilli, and also exhibited anaerobic growth. Four of these showed gas formation in deep dextrose agar and produced stormy fermentation in milk. One cubic centimeter of the broth culture of each of the seven nonmotile organisms was injected intramuscularly into guinea-pigs. Three of these animals survived with no demonstrable lesion being produced.

Of the four animals given injections with the cultures that produced stormy fermentation in milk, two showed evidence of gas formation and

11. Bergey, David H.: Manual of Determinative Bacteriology, ed. 3, Baltimore, Williams & Wilkins Company, 1930, p. 430.

edema. One of these died within forty-eight hours; the other survived with no necrosis or ulceration. The patients from whom these two cultures were obtained were both housewives residing in the city (dispensary nos. 599309 and 596769). The two remaining animals died, three and four days following injection, but neither showed evidence of gas bacillus infection. Unfortunately these two guinea-pigs were extremely emaciated and unsuitable for experimental purposes, but were used, of necessity, as no others were available. It is impossible to state whether or not these organisms were pathogenic, but as the cultural characteristics were those of *Clostridium welchii*, they are included as positive cultures. One of the patients from whom these cultures were obtained was a waitress, the other a mechanic (dispensary nos. 599367 and 599349, respectively). Thus, from the fifty-two cultures of normal skin there were four (7.67 per cent) in which *Clostridium welchii* was present.

UBIQUITY OF CLOSTRIDIUM WELCHII

It will be noted that the terms *Clostridium welchii*, *B. aerogenes-capsulatus*, *B. perfringens* and the Welch bacillus, are all used in this paper to designate the same organism. The term *Clostridium* is applied to the genus of spore-bearing anaerobes of the family of Bacillaceae (Bergey).

The organism known as *Clostridium welchii* was described by Welch¹² in 1892, under the name of *B. aerogenes-capsulatus*. The name *B. welchii* was suggested by Migula (1900). The same organism was described and called *B. phlegmonis-emphysematosae* by Eugene Fraenkel (1893), *B. perfringens* by Veillon and Zuber (1898) and *B. saccharobutyricus-immobilis* by Schattenfroth and Grassberger (1900). Although all of the synonyms are found in the literature, the terminology accepted by American bacteriologists is *Clostridium welchii* (Bergey).

Clostridium welchii is found in the gastro-intestinal tract of man and of practically all animals, both herbivorous and carnivorous. It is found extensively in soil and constantly in sewage. Members of this group have been isolated from gallstones, bile (Dayton, Gilbert and Lippmann,¹³ Williams¹⁴), shot-gun wads, woolen clothing and blankets

12. Welch, W. W., and Nuttall, G.: A Gas-Producing Bacillus (*B. Aerogenes Capsulatus*) Capable of Rapid Development in the Blood Vessels After Death, Bull. Johns Hopkins Hosp. 3:1 (July) 1892.

13. Gilbert, A., and Lippmann, A.: Le microbisme biliaire normal, Compt. rend. Soc. de biol. 55:157, 1903.

14. Williams, P. F.: A Bacteriologic Study of the Human Bile, New York State J. Med. 93:934 (May) 1911.

(Gage,¹⁵ Fleming¹⁶). Of particular interest is Meleney's¹⁷ report of finding 38 instances of pathogenic, gas-producing anaerobes in 83 cultures made of raw surgical catgut. Numerous observations made during the World War were to the effect that the Welch bacillus was frequently found in wounds in which there was no evidence of gas gangrene. Of 890 wounds studied at Evacuation Hospital no. 8, A. E. F., 478, or 53 per cent, contained anaerobic bacilli of the Welch group. Of these, 321, or 67 per cent, at no time showed evidence of gas gangrene.¹⁸

Raymond and Veight,¹⁹ studying the bacterial flora of war wounds, examined the surface exudate in 137 consecutive cases and found *Clostridium welchii* present in 23 per cent. Definite gas infection was present in 2.9 per cent, and 5.1 per cent if the doubtful cases were added. Of the cases in which *Clostridium welchii* was found on culture, there was definite gas infection in 13 per cent, adding the doubtful cases, the percentage was 22.5 per cent.

Stoddard²⁰ stated that studies by Fleming in 1914-1915 showed the presence of *Clostridium welchii* in 81 per cent of 127 wounds from one to seven days old, in 34 per cent of 56 wounds of eight to twenty-one days and 18.5 per cent of wounds more than twenty-one days old. The same author stated that Plisson found a harmless persistence of *Clostridium welchii* until the tenth day in 22 of 180 cases.

Tulloch,²¹ who made a detailed study of war wounds for the British Committee on anaerobic wound infections, found "light anaerobic infection in fourteen instances, no anaerobic infection in twenty-nine instances" in forty-three wounds in which delayed healing occurred. In another series of cases in which swabs were taken seven days before the wounds had healed sufficiently for the patient to be

15. Gage, F. M.: Gas Bacillus Infection—A Frequently Unnoticed Source in Civil Life, *Am. J. Surg.* **1**:177 (Oct.) 1926.

16. Fleming, Alexander: Some Notes on the Bacteriology of Gas Gangrene, *Lancet* **2**:376 (Aug. 7) 1915.

17. Meleney, F. L., and Chatfield, Mabel: How Can We Insure the Sterility of Catgut? *Surg., Gynec. & Obst.* **50**:271 (Jan.) 1930; Sterility of Catgut in Relation to Hospital Infections, *ibid.* **52**:430 (Feb.) 1931.

18. Callender, G. R., and Coupal, J. F.: Pathology of Gas Gangrene Following War Wounds, in Medical Department of United States Army in the World War, Washington, D. C., Government Printing Office, 1929, vol. 12, sect. 2.

19. Raymond and Veight: Bacterial Flora of War Wounds, *Bull. et mém. Soc. méd. d. hôp. de Paris* **41**:1302, 1917.

20. Stoddard, James L.: The Occurrence and Significance of *B. Welchii* in Certain Wounds, *J. A. M. A.* **71**:1400 (Oct. 26) 1918.

21. Tulloch, W. J.: Report of Bacteriological Investigation of Tetanus Carried Out on Behalf of the War Office Committee for the Study of Tetanus, *J. Hyg.* **18**:104 (Aug.) 1919.

considered convalescent, the following results were obtained: (a) no anaerobes in nineteen instances, (b) light anaerobic infection in twenty instances and (c) heavy anaerobic infection in four instances. It is not clear whether Tulloch uses the term "infection" advisedly in referring to his results, for it is obvious that anaerobes may be present in a wound without evoking an infection.

COMMENT

The fact that *Clostridium welchii* is found so frequently in an environment with which one is in daily contact may seem to detract from the significance of its occurrence in chronic ulcerating lesions. The evaluation of the result of this study is made difficult because of an insufficient knowledge of the various factors that are necessary for the production of a clinical picture of gas gangrene. Some of the factors, other than the presence of the organism, probably involve bacterial symbiosis, local tissue phenomena, which include circulatory status, and biologic and chemical defense mechanisms. The virulence of the bacterial strain, its toxin-producing ability and the degree of anaerobiosis in which the organisms are situated are also important considerations. No attempt will be made here to evaluate these diverse influences that determine pathogenicity. That these factors are necessary is suggested by the opinion of Welch,²² who made the first detailed description of the organism which he called *Bacillus aerogenes-capsulatus*. He said, "there is good reason to believe that intact tissues of human beings in health possess marked resistance to the gas bacillus." Emery²³ commented on the paradox that in a clinical case of gas gangrene, the organism is apparently very virulent, while "under ordinary circumstances the organism is almost non-pathogenic." Taylor,²⁴ who had a large experience with gas gangrene during the World War, and who has contributed much to the knowledge of the subject, expressed his belief that "the organism is essentially a saprophyte."

The literature on this subject does not contain many references to civil experiences with postoperative gas bacillus infections. In 1927, Tanner²⁵ first pointed out the potential danger of gas gangrene com-

22. Welch, W. W.: Morbid Conditions Caused by *B. Aerogenes Capsulatus*, Bull. Johns Hopkins Hosp. **11**:185 (Sept.) 1900.

23. Emery, W. d'Este: Some Factors in the Pathology of Gas Gangrene, Lancet **2**:948 (May 7) 1916.

24. Taylor, Kenneth: Factors Responsible for Gaseous Gangrene, Lancet **1**:123 (Jan. 15) 1916; Observations on the Pathology and Bacteriology of Gas Gangrene, J. Path. & Bact. **20**:384 (April) 1916; Gas Gangrene, Its Course and Treatment, Bull. Johns Hopkins Hosp. **26**:297 (Oct.) 1916.

25. Tanner, E. K.: Gas Bacillus Infections Complicating Senile and Diabetic Gangrene, S. Clin. North America **7**:1099 (Aug.) 1927.

plicating preexisting gangrene, and reported seven cases. Five of his cases showed no clinical evidence of gas bacillus infection prior to amputation. Linton (1930) emphasized the importance of this complication in the presence of any type of gangrene, and reported six additional cases. In only two cases of the six was gas bacillus infection detected prior to operation. Blake and Lahey²⁶ reported a case of infection with *B. aerogenes-capsulatus* (*Clostridium welchii*) which developed following amputation for diabetic gangrene. My experience with gas bacillus infections includes three cases complicating preexisting gangrene and information on two cases that developed elsewhere. There have undoubtedly been many unreported cases.

The route of infection in the cases presented and in those reported by Tanner and by Linton is not clear. Tanner attempted to isolate the organisms from the vessels of an amputated extremity and failed, but he said, "We feel sure they must have spread up the leg by way of the vessels or lymphatics to the site of amputation." Linton suggested as a possible mode of spread the thrombosed veins or lymphatics, "the organisms being in a quiescent state and stimulated to activity by trauma or other circumstances attending the amputation." Whether or not the organisms or spores may be in the tissues in a dormant state is a controversial point. Orr and Rows²⁷ found that bacteria left in contact with a nerve trunk ascended by the neural lymphatics as far as the cord, and could be found spreading along the posterior nerve roots. Teale and Embleton²⁸ found that spores inoculated into an animal may develop into vegetative forms and remain unphagocyted for a long time. In spite of reports of bacteria being found in normal tissues (Ellis and Dragstedt,²⁹ Reith,³⁰ Andrews and others³¹), the prevailing opinion is that this occurrence is not frequent. If the opinion that bacteria may be present in normal tissues is not accepted, the possibility exists of organisms being present in thrombosed veins and lymphatics or in

26. Blake, J. B., and Lahey, Frank: Infections Due to the *Bacillus Aerogenes Capsulatus*, With a Report of Ten Cases, *J. A. M. A.* **54**:1671 (May 21) 1910.

27. Orr, David; and Rows, R. G.: Toxic Infection of the Central Nervous System; A Clinical and Experimental Investigation, *Edinburgh M. J.* **17**:78 (Aug.) 1916.

28. Teale, F. N., and Embleton, Dennis: The Paths of Spread of Bacterial Toxins, with Specific Reference to Tetanus Toxin, *J. Path. & Bact.* **23**:50 (Oct.) 1919.

29. Ellis, James C., and Dragstedt, Lester K.: Liver Autolysis in Vivo, *Arch. Surg.* **20**:8 (Jan.) 1930.

30. Reith, Allen T.: Bacteria in the Muscular Tissues and Blood of Apparently Normal Animals, *J. Bact.* **12**:367, 1926.

31. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: Causation of *B. Welchii* Infection in Dogs, with Sterile Bile Liver Extract and Bile Salts, *Proc. Soc. Exper. Biol. & Med.* **28**:136 (Nov.) 1930.

cicatricial tissue resulting from inflammation. Phocas,³² Bazy and others made note of the occurrence of infections following surgical procedures, in which they attributed the infection to an activation of organisms latent in the tissues. Lecene and Frouin,³³ in a study of "latent microbes in the scar tissue of war wounds," found organisms in twenty-one of twenty-four wounds examined. All of these wounds contained foreign bodies, which introduces another factor; however, in four instances the foreign bodies were sterile while the surrounding fibrous capsule yielded cultures of divers organisms. These observations and the proposed route of infection as suggested by Tanner and Linton must have further confirmation, but it is probable that some such mode of infection was responsible for the cases reported here.

If this was not the method by which the gas bacillus entered the amputation stump, it must be assumed either that there was contamination from the skin of the patient or contamination from the catgut employed, or that the organisms reached the amputation stump from the intestinal tract. It is felt that the method of skin preparation was adequate to eliminate skin contamination. The catgut was of the same lot used in other operative procedures during the same period, none of which resulted in a gas bacillus infection. The intestinal route was suggested by Blake and Lahey as being responsible for their case following amputation for diabetic gangrene. The route is also suggested in a gas bacillus infection complicating a case of agranulocytosis, recently reported by Warr.³⁴ Weinberg, who has written a monograph on gas gangrene, expressed the belief that this route is a probable one, but this is at present a hypothesis.

Significance of Results.—One would be considered an alarmist to suggest that all chronic ulcerating lesions are potential cases of gas gangrene, for clinical experience does not warrant any such assumption. In none of the cases from which anaerobes were obtained did clinical evidence of gas gangrene develop. Most of the varicose ulcers were on extremities into which various solutions were being injected for the obliteration of varicose veins, but there is no recorded evidence that gas gangrene ever followed such a procedure. Two of the varicose ulcers (cases 7 and 23) that yielded virulent organisms were being treated by the application of sponges and tight elastic bandages. This procedure should produce approximate local anaerobic conditions and

32. Phocas: Le reveil de l'infection des plaies par l'acte chirurgical, Bull. et mém. Soc. de chir. de Paris 51:1933 (Oct.) 1915.

33. Lecene, P., and Frouin, A.: Nouvelles recherches demontrant la réalite du microbisme latent dans les plaies de guerre cicatrisées, Compt. rend. Acad. d. sc. 162:722 (May) 1916.

34. Warr, Otis S.: Agranulocytosis: Case with Terminal Gas Bacillus Infection, J. A. M. A. 96:507 (Feb. 14) 1931.

favor the persistence of the bacilli. As far as can be determined, no gas bacillus infections have resulted from this type of treatment.

However, we know that gas gangrene does follow operative intervention directed to the removal of chronic ulcers; that 34.37 per cent of chronic ulcers harbor the Welch bacillus, and the relationship between their presence and the surgical procedure is suggested. Tulloch's attitude as to the significance of the presence of the anaerobes in wounds may be adopted. He said:

One cannot assume that the presence of anaerobes, even in the later phases of the process of repair, are of no significance; for the presence of the bacilli of the Welchii group, *Vibrio Septique*, of *B. Edematiens*, and of *B. tetani* must always be a menace.

Gas gangrene as presented to the surgeon is usually a virulent, rapidly spreading type of infection accompanied by high mortality rate, approximately 40 per cent. In the two cases presented, although the gas bacillus infection was not the direct cause of death, it obviously was an important contributory factor. In the light of this experience, it is believed that whenever amputation is contemplated in a case in which an ulcerating lesion exists, the lesion should be cultured for anaerobes, and, if present, that polyanaerobic or specific antitoxin be given before operation. This opinion has previously been briefly expressed.³⁵

Status of Anaerobic Antitoxins.—Because of the apparent hesitancy on the part of the medical profession to accept the value of anaerobic antitoxins in prophylaxis and treatment, digression will be made here to refer briefly to its present status. From 1910, when Rosenthal first attempted to prepare a serum against *B. welchii*, until 1916-1917, there was practically no activity in this field. The increased incidence of gas gangrene, as a result of the World War, stimulated further investigations, and the names of Weinberg and Sequin,³⁶ Bull,³⁷ Sacquepee, Leclainche, Henry,³⁸ Bullock and others are written into the chapter on the early development of the anaerobic antitoxin.

Some of the most convincing evidence that the antitoxins are of value is found in their use experimentally in animals. It is possible, by

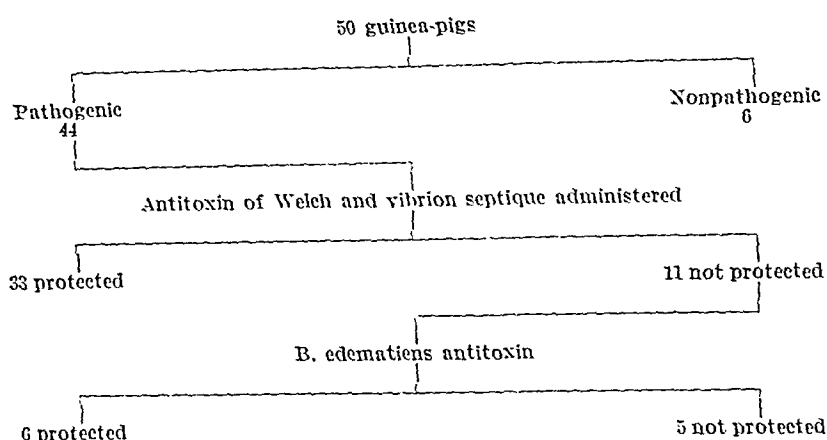
35. Manson, M. H.: Treatment of Tetanus and Gas Gangrene, Minnesota Med. 14:142 (Feb.) 1931.

36. Weinberg, M., and Sequin, P.: La gangrène gazeuse, Monographies de l'Institute Pasteur, Paris, 1918.

37. Bull, C. G.: Antitoxin for Gas Gangrene, New York State J. Med. 106: 821 (Nov.) 1917; *B. Welchii* Infections and Intoxication, J. A. M. A. 68:1815 (June 16) 1917. Bull, C. G., and Pritchett, Ida: Toxin and Antitoxin of and Protective Inoculation Against *B. Welchii*, J. Exper. Med. 26:119 (July) 1917; Antitoxin for *B. Welchii*, *ibid.* 26:603 (Oct.) 1917.

38. Henry, Herbert: On the Antitoxin Content of Some Gas Gangrene Sera Used in the Later Stages of the War, J. Path. & Bact. 23:270 (June) 1920.

using appropriate mixtures of antitoxin, to construct in a guinea-pig a sort of filtering mechanism, which will inhibit the development of certain organisms in the animal, and which will, at the same time, allow the growth of a pathogenic anaerobe against which no specific protection has been induced. Henry and Lacey³⁹ inoculated fifty guinea-pigs with cultures obtained from cases of gas gangrene. The following diagram shows the procedure and results:



Of the five nonprotected pigs, the cultures showed three infected with *Clostridium fallax* and two unidentifiable organisms.

Clinical evidence resulting from war experiences is offered by Sacquepee, who gave antitoxin to 319 wounded men, with a resulting incidence of gas gangrene of 1.17 per cent. In a controlled series, he reported the incidence as 7.2 per cent. In a series of 191 developed cases, the mortality in the patients treated with polyanaerobic antitoxin was 13.9 per cent, while in the same region the untreated patients showed a mortality of 75 per cent. Ivens⁴⁰ gave a polyanaerobic antitoxin to 433 wounded men among whom there were 30 cases of gas gangrene when first seen. In this series there was one death.

Opportunity for clinical verification of the efficacy of antitoxin is not frequent in civil practice and it will take time for statistics of this nature to become available. Morris, Gage, Baldwin and Gilmour,⁴¹ Larson and Pulford⁴² and other American authors all have written

39. Henry, H., and Lacey, Margaret: On the Anaerobes Responsible for Gas Gangrene in Man, *J. Path. & Bact.* **23**:281 (June) 1920.

40. Ivens, F.: Preventive and Durative Treatment of Gas Gangrene by Mixed Serum, *Brit. M. J.* **2**:425 (Oct. 19) 1918.

41. Baldwin, J. H., and Gilmour, W. R.: A Study of Gas Gangrene in Civil Surgery, *Ann. Surg.* **85**:161 (Feb.) 1927.

42. Larson, E. E., and Pulford, E. S.: Gas Gangrene of the Extremities with Especial Reference to Trivalent Anaerobic Serotherapy, *J. A. M. A.* **94**:612 (March 1) 1930.

on the subject since the war and urged that antitoxin be used. Kling⁴³ showed experimentally that antitoxin that is available on the market at the present time is efficient in neutralizing the antitoxins. The proposal of Williams,⁴⁴ in 1926, that the toxic symptoms of intestinal obstruction are caused by *B. welchii* toxins, has led to the use, in some places, of *Bacillus perfringens* antitoxin for this condition. It has been shown that it is of no value in intestinal obstruction, most recently and convincingly by Thurston⁴⁵ (1931), but this should in no way detract from its use in gas gangrene.

In an article on gas gangrene, Goodman⁴⁶ said:

Death from tetanus would seem unpardonable on account of neglect of a prophylactic dose of serum administered in a case of street injury. Nevertheless, it appears that one of the most potent therapeutic measures discovered as a result of the recent world war is either forgotten or we have not had an epidemic of this gas infection brought home to us, to the realization that prophylactic measures might be applied to prevent the occurrence of such disaster.

Larson and Pulford (1930) reported seven cases of gas gangrene in which the anaerobes were controlled in every instance. Only one amputation was done; this patient died of hemolytic streptococci septicemia. In every case trivalent anaerobic serum was given, and the authors believe that serotherapy contributed largely to the success in their cases.

Experience at the University Hospital with anaerobic antitoxins in gas bacillus infections has been very encouraging. It undoubtedly aided or made possible the recovery in two cases, in one of which cultures of *Clostridium welchii* were obtained from the muscle on the proximal side of the amputated extremity, and also from the blood stream at the time of operation. In the other, a postoperative case of disarticulation of the hip joint, in which surgical treatment of the infection consisted only of reopening the wound and the intravenous administration of *Bacillus perfringens* antitoxin, a rapid recovery ensued. It is to be emphasized that antitoxin should be used to supplement, rather than to supplant, surgical treatment in a clinical case of gas bacillus infection.

The surgical treatment for gas gangrene is fairly well established, but for the sake of completeness, a summary of the essentials will be

43. Kling, David: Treatment of Gas Gangrene with Normal Horse Serum, *Ann. Surg.* **91**:261 (Feb.) 1930.

44. Williams, B. W.: The Importance of Toxemia Due to Anaerobic Organisms in Intestinal Obstruction and Peritonitis, *Brit. J. Surg.* **14**:295, 1926.

45. Thurston, Herbert F.: The Rôle of Toxins of *B. Welchii* in the Toxemia of Acute Intestinal Obstruction, *Arch. Surg.* **22**:72 (Jan.) 1931.

46. Goodman, Charles: Gas Gangrene, *Ann. Surg.* **79**:806 (June) 1924.

made. In cases of massive infection, with involvement of an entire extremity, amputation is the accepted method of treatment. A tourniquet should not be used, no attempt should be made to form flaps and the stump must be left open. Meticulous care should be used to minimize trauma to muscle tissue while securing blood vessels. There is no necessity for retraction with sharp hooks or retractors. The exposed surface may be lightly covered with gauze saturated with some oxidizing agent such as surgical solution of chlorinated soda or dichloramine T. Secondary plastic operations may be necessary to make a satisfactory stump.

In localized infections, where the longitudinal spread of the process is confined to single muscle groups, excision of the involved muscle may suffice. Excellent results have been reported in this type of case by Frankau, Drummonds and Neligan,⁴⁷ Ivens,⁴⁸ Kellogg Speed⁴⁹ and Larson and Pulford.⁴²

Good surgical judgment in the selection of cases is necessary. The criteria for resection are the color, contractibility and bleeding of the muscles.

Blood transfusion may be a life saving measure following amputation or débridement for gas gangrene.

SUMMARY

Two cases are presented in which gas gangrene followed amputation of extremities that were the site of chronic ulcers. Their similarity led to the question of the relationship of chronic ulcers and gas gangrene and the frequency with which ulcers harbor pathogenic anaerobes. Cultures of thirty-two ulcerating lesions revealed that eleven, or 34.37 per cent, harbored pathogenic gas-producing anaerobes. Fifty-two control cultures of normal skin yielded four cultures (7.6 per cent) of *Clostridium welchii*.

Clostridium welchii is the most frequent pathogenic anaerobe found in chronic ulcers. Gas gangrene complicating preexisting gangrene has previously been emphasized, and it is suggested that vigilance be extended to include chronic ulcers as a possible source of gas gangrene following surgical intervention. The possible routes of infection have

47. Frankau, C. H. S.; Drummonds, H., and Neligan, G. E.: Successful Conservative Treatment of Early Gas Gangrene in Limbs by Resection of Infected Muscles, *Brit. J. Surg.* **1**:729, 1917.

48. Ivens, F.: Clinical Study of Anaerobic Wound Infection and Analysis of 107 Cases of Gas Gangrene, *M. Press* **103**:12, 1917.

49. Speed, Kellogg: Localized Gas Infection Treated in War Wounds by Muscle Group Excision, *J. A. M. A.* **70**:225 (Jan. 26) 1918.

been discussed and it is believed that the most likely explanation is that the organisms were in the tissues prior to amputation. This opinion is speculative and requires definite evidence to corroborate it. Poly-anaerobic and *Bacillus perfringens* antitoxin has definite merit and should be more widely used. It is suggested that chronic ulcerating lesions be cultured by the use of milk as a medium, if surgical intervention is to be directed to their removal. If the characteristic stormy fermentation produced by *Clostridium welchii* is obtained, anaerobic antitoxin should first be administered.

ACUTE AND SUBACUTE ATROPHY OF THE LIVER AND THE EVOLUTION OF TOXIC CIRRHOSIS

A REVIEW OF TWENTY-TWO CASES *

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This paper is based on a clinical and pathologic study of twenty-two cases of atrophy of the liver. The cases have been selected as characteristic of the type of atrophy commonly designated as yellow or red atrophy of the liver (Rokitansky), and are illustrative, both clinically and pathologically, of the various stages of this type of hepatic disease.

GENERAL COMMENT

Classification.—Based on anatomic considerations, the three stages or degrees of atrophy of the liver¹ are: acute, subacute and chronic. The microscopic anatomy seen in the acute stage was characterized by extensive necrobiosis of the hepatic cells. The subacute stage followed when clearing of the cellular detritus of the acute cytolytic process appeared completed; this left a disorganized liver in which there was only partial preservation of the parenchyma. Owing to the extensive loss of hepatic cells, the hepatic stroma was brought into prominence. The chronic stage was characterized by progressive shrinkage of the dismantled hepatic stroma and likewise by regenerative rather than retrogressive changes of the parenchyma. In the latter part of the chronic stage, well defined, coarsely nodular cirrhosis was revealed. This is the end-stage or the stage of healing of acute atrophy of the liver, to which Mallory's² designation "toxic cirrhosis" may be applied. A consideration of the relation of this form of cirrhosis to others is not within the scope of this paper.

In an attempt to correlate this pathologic classification with the clinical features of the disease, only partial success was met with. The

* Submitted for publication, July 14, 1931.

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1. Marchand, F.: Ueber Ausgang der acuten Leberatrophy im multiple knotige Hyperplasia, Beitr. z. path. Anat. u. z. allg. Path. **17**:206, 1895.

2. Mallory, F. B.: Cirrhosis of the Liver; Five Different Types of Lesions from Which It May Arise, Bull. Johns Hopkins Hosp. **22**:69 (March) 1911.

apparent duration of the disease, as judged by the duration of jaundice or other significant symptoms, was at considerable variance in some instances with the anatomic changes in the liver. In one case of our series, in which jaundice was of sixteen days' duration, the lesion was anatomically acute, whereas in another case, with three days of jaundice, the lesion was, by the same criteria, of a late, subacute type. Likewise, in the chronic stage, it was sometimes entirely impossible to reconcile the clinical duration with the anatomic features, as, for example, in two cases in which the lesions appeared older than the history of symptoms indicated them to be.

Inability to correlate the symptomatic age of the lesion with the anatomic age emphasizes that even in this form of hepatic atrophy considerable destructive change may occur in the liver before clinical evidence of hepatic disease appears. The degenerative process in the liver may progress to the stage just less than the maximal subclinical level, and then with a minimal added insult the hepatic disease may become manifest. If the disease is of sufficient severity, the clinical picture of icterus gravis will be evoked, but the anatomic changes characteristic of rapid hepatic atrophy may not be found. Similarly, in other cases, the disease may progress with equal slowness before it is clinically evident, as well as in the clinical phase, and reveal at the end lesions much older than seem possible when the duration of symptoms is considered. Life may endure in the acute phase, as was illustrated in one of our cases, for a considerable period (sixteen days), with coexisting extensive necrosis of the hepatic parenchyma.

Although it is impossible accurately to foretell the exact state of the liver, as judged by the duration and severity of the symptoms, nevertheless a clinical classification should exist. The only approach to this must be on the basis of duration and severity of symptoms; although they may not always be in accord with the anatomic features, they may give a relatively useful indication to the clinician of the stage of the disease. Since jaundice is the most constant symptom that these patients present, it is perhaps the best clinical guide. Ascites is relatively latent and always denotes, according to the anatomic classification we have used, a chronic stage.

We observed only one case of acute atrophy, and in this the duration of symptoms was sixteen days. Nine cases of the subacute stage, with the clinical duration of from three to thirty-four days, were reviewed. Twelve cases were of the chronic group. In these cases the clinical duration was from thirty-two days to three years. The average life expectancy for the entire series of cases, as based on the duration of jaundice, was fifteen weeks. Fifteen of the twenty-two patients, however, died two months after jaundice first appeared.

ETIOLOGIC CONSIDERATIONS

Although many different etiologic agents have been found associated with acute atrophy of the liver and with the related subacute and chronic types, the pathologic anatomy in cases of differing causation is similar. Variations in the anatomic picture are chiefly quantitative. Most cases of hepatic atrophy, in spite of the large number of substances reported as etiologic factors, develop without adequate etiologic explanation. Whether all cases will eventually be shown to be due to an exogenous toxic substance is doubtful. Endogenous or metabolic toxins may eventually prove to be of decided importance.

It is apparent from a careful analysis of cases, especially those due to a known agent, that in addition to the toxic factor, some fundamental unknown constitutional state, perhaps transient and of metabolic character, also enters into the etiology and pathogenesis. This fact is shown by the varying degrees of susceptibility patients exhibit to toxic substances which are known sometimes to induce hepatic atrophy. In experimentally produced hepatic necrosis, Opie and Alford,³ Graham,⁴ Davis and Whipple⁵ and Simonds⁶ have shown that the available dextrose and the hepatic glycogen afford considerable protection to the liver against injury, and, further, that regeneration progresses more favorably when carbohydrate is abundantly supplied in the diet. This may explain in part the varying degrees of susceptibility that patients exhibit.

Of the substances reported to produce these hepatic changes in man or animals may be mentioned cinchophen, chloroform, mercury, arsphenamine, arsenic, phosphorus, trinitrotoluene, trinitrophenol, tetrachlorethane, dinitrobenzene, Aspidium, lupine toxins, *Amanita phalloides* toxin, carbon tetrachloride, chiniofon (N. N. R.), toxic hyperthyroid states, toxic products of pregnancy, bacterial toxins, alcohol in large quantities, hemagglutinative serums and cystine.

A toxic substance as an etiologic factor could be found in seven of our cases. In five cases it was cinchophen, and in two cases arsphenamine. In the remaining fifteen cases a definite etiology could not be established. Of possible significance, in relation to antirheumatic drugs,

3. Opie, E. L., and Alford, L. B.: The Influence of Diet on the Hepatic Necrosis and Toxicity of Chloroform, *J. A. M. A.* **62**:895 (March 21) 1914.

4. Graham, E. A.: The Resistance of Pups to Late Chloroform Poisoning in Its Relation to Liver Glycogen, *J. Exper. Med.* **21**:185 (Feb. 1) 1915.

5. Davis, N. C., and Whipple, G. H.: The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, *Arch. Int. Med.* **23**: 612 (May) 1919.

6. Simonds, J. P.: The Mechanism of the Protective Action of Carbohydrate Diets in Phosphorus and Chloroform Poisoning, *Arch. Int. Med.* **23**:362 (March) 1919.

is the fact that besides the five cases in which there was a history of some type of rheumatic, arthritic or neuritic pain, and in which there was a history of the patient having taken cinchophen for its relief, there were seven additional cases in which there was a similar history of pain, but in which there was no admission by the patient that drugs had been taken. The inference that might be drawn from this is that cinchophen, or proprietary preparations containing it, might have been used, but information of its use was not obtained from the patient. In only one of these seven cases was any type of treatment for the rheumatic pain admitted, and this was some form of intravenous injection of autogenous blood after it had been allowed to stand. The possibility that this might have been significant is shown by experiments of Pearce,⁷ and others, although somewhat different, who produced severe hepatic necrosis in animals by the injection of hemagglutinative serums.

In three cases the condition so closely followed acute respiratory infection that the possibility of the infection playing some part must be considered. In one case ^{7a} the patient had given a severe reaction to influenza vaccine three years before jaundice developed. In one case the hepatic condition followed shortly after operative intervention for ventral hernia, at which time a gallstone was removed from the gall-bladder, and it was noted that the liver was normal. If the hepatic changes followed the operation, the possibility of the anesthesia inducing the changes must be considered.

In four cases a clue to etiology could not be found, with the possible exception that in one case there was an ancient history of syphilis, but without clinical or pathologic evidence of its presence or any history of treatment, and that another case followed a severe emotional upset. The older writers believed the latter to be significant in the etiology.

The relation of concurrent disease involving the upper part of the intestinal tract is fairly striking. Seven patients complained of epigastric distress for a considerable time preceding the actual development of symptoms of hepatic atrophy. Three of these patients had duodenal ulcers; in one they were associated with cholelithiasis, and two other patients had cholelithiasis only. Two patients did not present

7. Pearce, R. M.: The Experimental Production of Liver Necroses by the Intravenous Injection of Hemagglutinins, *J. M. Research* **12**:329, 1904.

7a. In several places in this paper, the analytical reader will experience difficulty in adding the number of cases mentioned in different categories to a total that is consistent with that given for the group which includes those categories. The reason for this difficulty is that some cases necessarily have been mentioned twice. For instance, a patient who had arthritis also had infection and it was necessary to mention her once in connection with each condition. This apparent discrepancy seemed less objectionable than the circumlocution that would have been necessary to avoid it.

anatomic evidence that would account for the epigastric distress. Cholelithiasis or cholecystitis was also found in three other cases, but without history of previous epigastric trouble.

In one case, besides cinchophen, toxemia of pregnancy may have played a part, but this is the only case in which there was a probable relation to pregnancy.

In none of the cases was there alcoholic addiction, and in only five cases was the use of alcohol admitted.

In two cases only was there laboratory, clinical or pathologic evidence of syphilis.

Youth or an early adult age, as other investigators have found, was not a predisposing factor in this series of twenty-two cases, for the ages of the patients varied from 7 to 66 years, the average age being 48 years. Only two patients in the group were less than 30 years old.

The sex incidence shown in previously reported cases is maintained in this series, in which fourteen cases affected females and eight affected males.

CLINICAL ASPECTS

The symptoms were characterized by either a rapidly fulminating course advancing to death or a slowly progressive course. It is rather difficult for that reason to describe the cases as a whole. This is possible, however, if it is appreciated that the course of the disease may be completed in a few days, or that it may progress in a mild form with similar symptoms until severe hepatic insufficiency ensues. As a terminal manifestation the symptoms of acute, fulminating atrophy usually present themselves.

Initial Symptoms.—At the beginning of the illness, jaundice was present in twelve cases. In four cases it was the only initial complaint. As an accompaniment of icterus, pruritus was complained of by six patients, and seven had noted acholic stools and dark-colored urine. Malaise, suggested by lassitude, mental depression, headache, weakness or anorexia, usually an accompaniment of the jaundice, appeared in fifteen cases as a first symptom; malaise appeared as the principal initiating symptom without jaundice four times.

In eleven cases there were abdominal distress, usually a vague, mild abdominal pain, fulness in the epigastrium, flatulence, nausea or vomiting. In only three cases, however, was vomiting elicited in the history, and never hematemesis. In four cases pain over the region of the liver was definitely mentioned. As the only prodromal complaint, abdominal distress was recorded in three cases. In one case, chills and fever, with malaise and abdominal distress, were recorded as being the beginning of the illness. In only one case was the condition fulminating at the onset, progressing rapidly to death in four days.

Progressive Symptoms.—Although jaundice was found in only twelve cases as an initial symptom, its development in our cases became universal with progression. In the cases in which it was delayed, judged by the apparent clinical beginning of the trouble, it became evident in from one to thirty-five days after the onset of illness; the average period before its appearance was thirteen days. In five cases there was history of some fluctuation of the icterus, usually with one period of remission, but in none did the pigment completely leave the skin or sclera. In one of the cases all characteristics of the illness were subject to exacerbation and remission, and jaundice followed the same tendency. In all but these five cases, the degree of jaundice was progressive up to a maximal level, with some fluctuation of the curves of serum bilirubin at the higher levels, but without much corresponding change in cutaneous pigmentation. In all but five cases light-colored to clay-colored stools were observed, but frequently only in the terminal stages of the illness did the clay color of the stool correspond in degree to the relatively high values for serum bilirubin. Duodenal drainage and tests for bile in the stool usually gave evidence of the presence of bile, but in two instances duodenal drainage was negative for bile late in the course of the disease when earlier it had been positive. Pruritus as an accompaniment of icterus was found in only nine cases. A purpuric tendency was observed in five cases, although hemorrhages were almost always found at necropsy.

Since most of the patients came to the clinic late in the course of the disease, there was usually no difficulty in predicting the termination of the illness. In two cases, however, because of the apparently mild systemic reaction accompanying the icterus, the probability of the disease terminating fatally was not entertained. That in these cases the disease was of the simple catarrhal type was given further credence when the jaundice began to clear up. As events subsequently revealed, one patient was susceptible to cinchophen, and the remission experienced was probably due to discontinuance of the drug. On the patient's returning home, however, resumption of use of the drug caused exacerbation of hepatic changes, which progressed to a fatal termination. In one case there was no history of the patient's having taken drugs, and the icterus in the beginning was clearly not of the grave type. In one case it was fairly well established on the patient's first admission that the jaundice was the result of the toxic effect of oxyliodide, and although a guarded prognosis was given, this patient might have recovered had advice to discontinue the use of the drug been adhered to.

Since in many of our cases, illness developed and the patient died before the van den Bergh reaction was generally applied, readings of this reaction were obtained in only thirteen cases. In all of these the

reaction was direct. Values for serum bilirubin were obtained in the same number of cases. The degree of icterus, as judged by this quantitative procedure, usually appeared to be a criterion of prognosis and an indication of the condition that would be found in the liver at necropsy. In four cases jaundice seemed especially to correspond in its degree to the progress of the disease. The highest degrees of icterus were present, as a rule, in the cases in which the course was more rapid, especially in those terminating in the acute or early subacute stages, in which values for serum bilirubin up to 39 mg. for each 100 cc. of blood were sometimes shown. In some cases there was a fall from a previous high level as the patient entered the terminal stages of the disease.

Studies of blood coagulation time gave conflicting results in this series of cases. In some instances, its increase was substantially apparent with an unfavorable turn in the condition of the patient, but as a rule its tendency to increase was by no means as marked as in extrahepatic obstructive types of jaundice, and could not be relied on as a ground for predicting that hemorrhages would be found at necropsy.

In one case only was there a history of jaundice previous to that associated with the last illness.

As in the prodromal stages of the disease, and also in its progress, abdominal distress was often an annoying complaint. Anorexia, heavy feeling in the epigastrium, epigastric soreness, dull pain or light stitches of pain along the right costal margin, intolerance to food or nausea at some time, although this fluctuated to some degree, were present in all cases. In only fourteen of the cases did vomiting enter into this picture, and in only one case was there blood in the material vomited.

Although pain approaching the nature of colic, typical of intraductal occlusion by a calculus, was never observed with the appearance of jaundice, it did appear in the progress of the disease in seven cases. In four cases, it resembled closely the pain of colic from biliary calculus. In one of these, besides pain there were fever, leukocytosis and abdominal rigidity, which further added to the complications of diagnosis. In two cases there was accentuation of the jaundice with the attacks of colic, and in two cases morphine was required for relief of pain. In these respects there was similarity to the pain occurring in obstruction of the biliary ducts from calculus. Usually there was only one attack of pain, which disappeared without marked improvement in the jaundice and without leaving marked residual soreness. The opposite would have been expected had the pain been of the type produced by obstruction from a calculus. The rare association of chill and fever in cases of atrophy is a further differential sign. In one case only were calculi

found at necropsy as a basis for the pain, and in that case, although the gallbladder was filled with stones, evidence was not at hand to indicate that any of them had been passing through the ducts. It must be concluded from a review of our cases that pain as a feature of intrahepatic jaundice at times forms a rather conflicting picture, and serves to confuse the diagnostician who might suspect that the jaundice is due to obstruction of extrahepatic bile ducts by calculi.

In all cases dealt with in this group, weakness, progressing eventually to a state of exhaustion, constituted a significant part of the clinical state. In the subacute and chronic types of the disease this progression was slow and was subject to exacerbations and remissions that correspond with the general fluctuations of the disease. The extreme weakness was always the signal of impending hepatic insufficiency and the approach of a fatal state.

Loss of weight usually was noted by the patients, and was often related to loss of appetite. Hepatic atrophy apparently has no predilection for either the obese or the thin person, for extremes in weight in both directions were noted throughout the series of cases.

For the most part, these cases ran an afebrile course, or at least the temperatures were below 100 F., usually with some depressions below normal. In one case there were initial chill and fever for one day, and in another, with the reappearance of jaundice after remission, a temperature of 103 F. was experienced. During their stay in the hospital three patients had fever, but only in one case was this troublesome.

The pulse was little changed until signs of fatal hepatic injury became manifest as a part of the toxemia; then it became rapid and weak. Early in the disease slight slowing sometimes was observed.

Ten cases were observed in which there was tenderness over the liver or in the epigastrium. The liver was definitely small in eight cases. In three cases the reduction in size of the liver during observation was a noteworthy diagnostic and prognostic sign. In one of these, with the initial appearance of jaundice, the liver was thought to be reduced in size; several months later, after a remission and in a period of exacerbation, it appeared enlarged. But a few days later, it was again found to be reduced in size. Additional evidence was furnished in two cases that the liver may be larger than normal until a short time before the end. Too much emphasis as to diagnosis cannot be placed on the size of the liver, for in obstructive jaundice it will be found large at first and later smaller, although the reduction in size occurs perhaps with less rapidity than in atrophy.

Ascites was present in almost all of the cases of the chronic type. In one case (the earliest in which it appeared clinically), it was noted on the twenty-fifth day after the onset of symptoms; death occurred on

the thirty-second day of the illness. Ascites was observed in eight additional cases. Its absence in the case of three years' duration was the greatest contradiction to its constancy in delayed cases.

Neither severe constipation nor serious diarrhea was observed with any frequency. Perhaps the greater tendency was to constipation, but in one case severe diarrhea was complained of.

Estimations of the concentration of urea in the blood did not as a rule offer much help in estimating the severity of hepatic degeneration. In one case in which death occurred within four days after the onset, the value for blood urea was 24 mg. in each 100 cc. Exceedingly low figures were obtained in only two cases in which, on two analyses, values of only 9 and 10 mg. in each 100 cc., respectively, were found.

Values for blood sugar were below ordinary normal levels in only three cases, in which they receded to 50, 54 and 76 mg. in each 100 cc. The administration of dextrose in the treatment may have been to some degree responsible for maintenance of normal values in the other cases.

Urinalysis usually revealed albumin in moderate amount, but in seven cases none was found. Casts and erythrocytes were also occasionally found. The presence of blood was usually an indication, as confirmed at necropsy, of pelvic or vesical hemorrhage. Tests for bile in the urine were obviously always positive. Microscopic search for crystals of leucine and tyrosine was made in five cases, but these substances were never found.

Moderate to moderately severe grades of secondary anemia were frequently observed, but anemia was never an alarming feature, except in one case in which hemorrhage constituted the immediate cause of death.

The Terminal Stage.—For a variable period after the development of jaundice, weakness, malaise, anorexia and abdominal distress, the condition appeared to remain constant, with perhaps some tendency to temporary remissions or exacerbations, but without actually becoming much more severe. Usually the patients had remained at home until the inception of the terminal stages. They were more or less ambulatory and under the care of their local physicians, evidently not appreciating that eventually a critical turn in their course would come.

The initial and progressive stages may be exceedingly short in the fulminating cases, as in one case in which prodromal manifestations were present for only one day, or they may slowly progress for weeks, months or years. Reparative processes were so completed in one case that the illness for which the patient entered the clinic concerned only remotely that which related to hepatic atrophy. In this case the patient was suffering from carcinoma of the stomach, and directed her complaint almost entirely to this.

The progressive cases of jaundice, in which there was no tendency to improvement, sooner or later advanced into the serious stage of severe hepatic insufficiency. When this stage was reached, the prognosis became universally grave, for recovery did not occur. This turn was usually not abrupt, but gradual. Weakness was accentuated, progressing to exhaustion, the abdominal complaints became more troublesome, jaundice almost always became intensified, and changes in the mental state appeared. When finally hepatic insufficiency had progressed to a fatal state, mental changes appeared most marked, progressing through dulness to mental confusion, stupor and delirium. Semicoma, rapidly deepening to coma, always signified the end. With these changes there were sometimes generalized muscular twitchings or actual convulsions, as shown in six cases of the series. In one case hematemesis was severe. Fever, with a temperature of from 100 to 108 F., was present in thirteen cases as a terminal manifestation; in other cases the temperature was practically normal to the end. With the rising fever or other increased toxic manifestations, the pulse rate became rapid and feeble, and acceleration to from 100 to 140 beats a minute was the rule. In spite of the earlier low and normal values for blood urea in many cases, at this time there was a rise; in this series the maximal amount was 106 Gm. in each 100 cc. With this there was diminution of urinary output, which progressed in a few cases to almost complete suppression. In one case there was profuse sweating at the end. Leukocytosis sometimes accompanied this final stage; in five cases the leukocyte count ranged from 10,200 to 24,000.

The mean duration of this stage, from the time of appearance of its subjective signs until death, as nearly as could be estimated, was twelve and a half days; the spread was from one to thirty-three days. After the development of the more profound mental changes, duration of life was a matter of only a few days.

SURGICAL ASPECTS

The combination of pain with jaundice usually denotes obstruction of the common bile duct by a calculus. That this should be a not uncommon occurrence in the subacute and chronic stages of hepatic atrophy forms the most frequent justification for exploration. Although exploration has not proved to be of any particular value in cases of unmixed hepatic atrophy, and although there is some evidence that it has been harmful, there is, nevertheless, always the possibility that the surgeon may discover a condition such as the presence of gallstones; these, if found, really are responsible for the trouble, and removal will effect relief.

Other investigators have reported experiences similar to those met with in three cases of our series, in which the diagnosis of primary

hepatic atrophy was ascertained with certainty only by laparotomy. Umber,⁸ Huber and Kausch,⁹ Strauss,¹⁰ Braun,¹¹ Brütt,¹² Römer,¹³ Pool and Bancroft¹⁴ and Whipple¹⁵ have reported cases of this type.

Braun stated that in his experience drainage of bile causes much improvement. In Römer's case, marked improvement was exhibited after laparotomy; apparently the patient recovered completely. Whipple would not operate if the diagnosis could be clearly established by other means, although he thought it not harmful to prove the diagnosis in this way. The latter is probably the more acceptable position.

Probably the most significant differential diagnostic point distinguishing unmixed atrophy of the liver from obstructive lesions of the biliary tract is that in hepatic atrophy bile is persistently found in the material obtained by duodenal drainage of deeply jaundiced patients who usually have associated severe toxemia. Another significant fact shown by this study is that severe pain was never an initial accompaniment of the icterus, and chills and fever were extremely rare, having been recorded in only one case in the series with the onset of jaundice.

PATHOLOGIC ANATOMY

Macroscopic Changes.—In this series of cases, atrophy of the liver was the outstanding pathologic change observed on macroscopic examination. The smallest liver found in an adult weighed 640 Gm.; jaundice had persisted for twenty-nine days. The average weight of the livers for the entire group was 955 Gm., excluding the weight of a child's liver. Although atrophy was a distinctive characteristic, the weight of the liver was rather variable throughout the study. In the acute and early subacute cases, and to some extent in the cases of longer duration, the atrophy was not extreme. It appeared to reach its maximal low

8. Umber, F.: Zur Klinik der akuten beziehungsweise subakuten Leberatrophy, Deutsche med. Wchnschr. **1**:537 (May 15) 1919.

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11. Braun, W.: Chirurgische Eingriffe bei akuter und subakuter Leberatrophy, Klin. Wchnschr. **1**:2510 (Dec. 16) 1922.

12. Brütt, H.: Zur Frage der Spontanheilung der subakuten Leberatrophy, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **36**:29, 1923; abstr., J. A. M. A. **81**:259 (July 21) 1923.

13. Römer, C.: Beitrag zur Frage der Heilung der Leberatrophy, Virchows Arch. f. path. Anat. u. Physiol. **254**:229, 1925.

14. Pool, E. H., and Bancroft, F. W.: Atrophy of the Liver with Nodular Hyperplasia, Surg., Gynec. & Obst. **37**:44 (July) 1923.

15. Whipple, A. O.: The Clinical Course of Subacute Yellow Atrophy as Observed in Two Proven Cases, Am. J. Surg. **6**:655 (May) 1929.

level in three cases in which the atrophy was of the late subacute stage, and to be considerably increased in the early chronic stage, although in the subacute group there was considerable variation in weight from case to case. In the late chronic cases, there usually were uniformly small livers; except in two cases, the weight was well under 1,000 Gm. Atrophy frequently was more pronounced in the left lobe.

The color of the liver, even in the early cases, was variable. The pure yellow or pure red atrophy, as described by Rokitansky,¹⁶ rarely existed. In our cases there usually was a mottled red and yellow appearance. The yellow color, as it existed in the degenerating parenchymal units, frequently shaded to green, representing the oxidation of bilirubin to biliverdin. The red regions, which usually were extensive, represented the zones of total parenchymal destruction, with the detritus of the necrotic hepatic cells cleared away. The red was due to blood still circulating through these skeletonized lobules, and the shade of red apparently depended on the thoroughness of this continued circulation, for in the late cases with the impairment of circulation the color changed to grayish red.

The consistency of the livers was variable throughout the series. It appeared to depend on the degree of parenchymal destruction and on the amount of condensation of the hepatic framework. It also was found to vary with the size and number of the regenerating nodules. In the acute and early subacute cases, the entire liver was soft, later becoming leather-like and finally very firm. The Glisson capsule became opaque and thick.

Evidence exists to show that the yellow nodules, as seen in the cases of chronic atrophy, are an expression of parenchymal regeneration following destruction. The evolution of these nodules was well shown in cases of varying duration. The younger, regenerating nodules appeared as tiny yellowish or greenish-yellow portions, becoming evident as tiny flecks, or as ill defined individual or aggregated lobules in a reddish-brown ground substance that was devoid of lobular markings, except as central veins might demarcate the lobules in a liver that was the site of chronic passive congestion (fig. 1). Beneath the capsule they gave the liver a mottled or blotchy yellow appearance, or rose from the red, capsular surface as small yellow granules. The cut surface gave the same appearance, but the nodules were frequently seen more prominently gathered about visible blood channels. They were much more prominent in the right lobe than in the left. In the subacute stages, it was impossible to distinguish between the remains of the hepatic lobules and beginning regeneration. There was considerable

16. Rokitansky, Carl: *A Manual of Pathologic Anatomy*, London, Sydenham Society, 1849, vol. 2, p. 122.

variation in the degree of the nodular development; the nodules of larger size appeared in the late cases of chronic atrophy (figs. 2 and 3). In their late development, nodules from 0.5 to 2 cm. in diameter were the rule, although in some cases (figs. 4 and 5) the huge nodular development simulated the gross appearance of *hepar lobatum*.

Histologic Changes.—The composite histologic picture in this group of cases of atrophy consisted of three outstanding changes, namely, retrogression, regeneration and changes in the hepatic stroma. The predominating change depended on the stage or age of the lesion, that is, on whether it was acute, subacute or chronic. Throughout all of the stages there was extensive atrophy of the hepatic parenchyma, at first necrosis, then recovery of small groups of hepatic cells from the toxic influence and finally parenchymal replacement through regeneration.

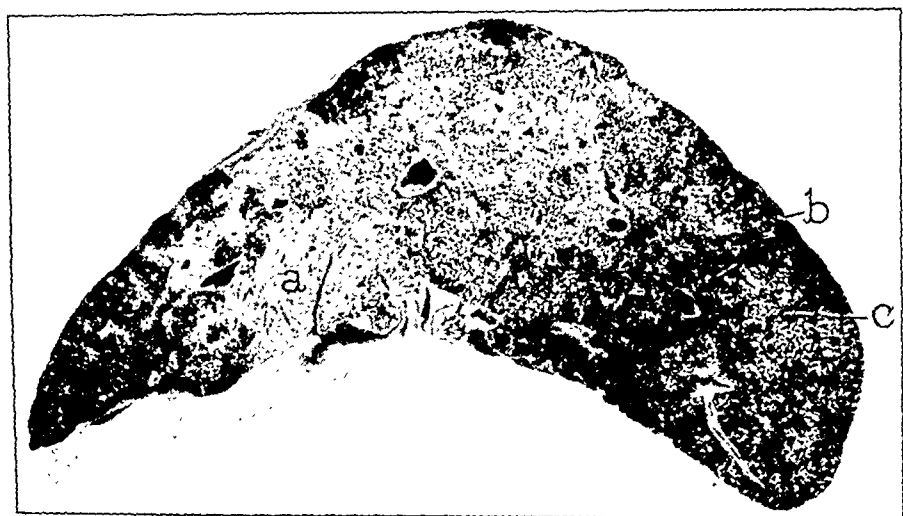


Fig. 1.—Early chronic atrophy of the liver. The light areas (a) represent the zones of complete parenchymal destruction, with contraction of the hepatic stroma ("red atrophy"). Congested skeletonized lobules are represented by the dark areas (b). Beginning regeneration of hepatic parenchyma is shown in the form of small nodules (c).

Since the prominence of the connective tissue was due to loss of hepatic cells, the framework of the liver thus being brought into view, the changes in it also followed with the age of the lesion; at first there was a network of reticulum; later this contracted to present the appearance of fibrosis. The toxic effects were apparently directed solely against the hepatic cells. The bile ducts were preserved, and the connective tissue structures withstood the insult without reacting to it. Since the connective tissue of the liver was uninjured, its part as a replacement tissue was mostly passive.

In the acute stage the parenchymal retrogressive changes dominated the picture. Various stages of cellular degeneration, to extensive necro-

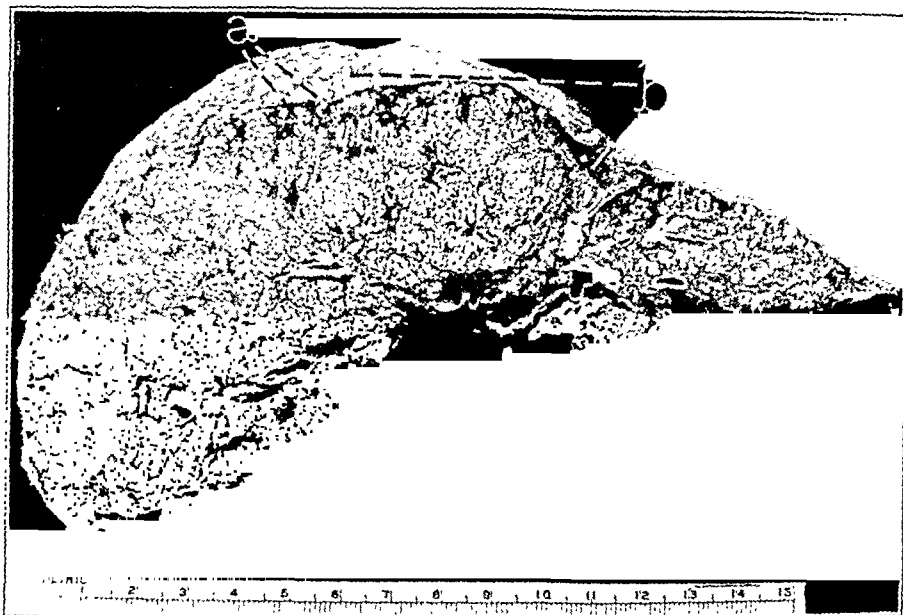


Fig. 2.—Chronic atrophy of the liver (early toxic cirrhosis); (a) regenerated nodules of hepatic parenchyma; (b) hepatic stroma somewhat contracted (“red atrophy”).

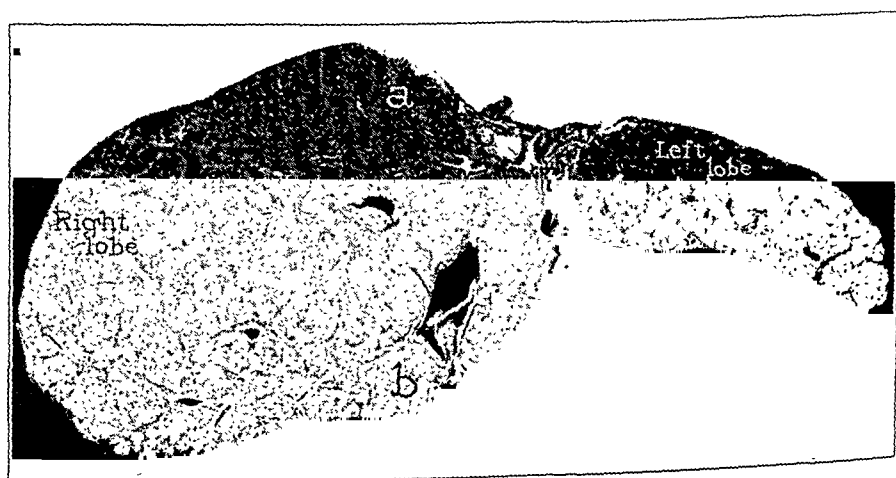


Fig. 3.—Chronic atrophy of the liver (toxic cirrhosis); (a) large red area devoid of parenchyma, consisting of contracted hepatic stroma; (b) nodules of regenerated hepatic parenchyma.

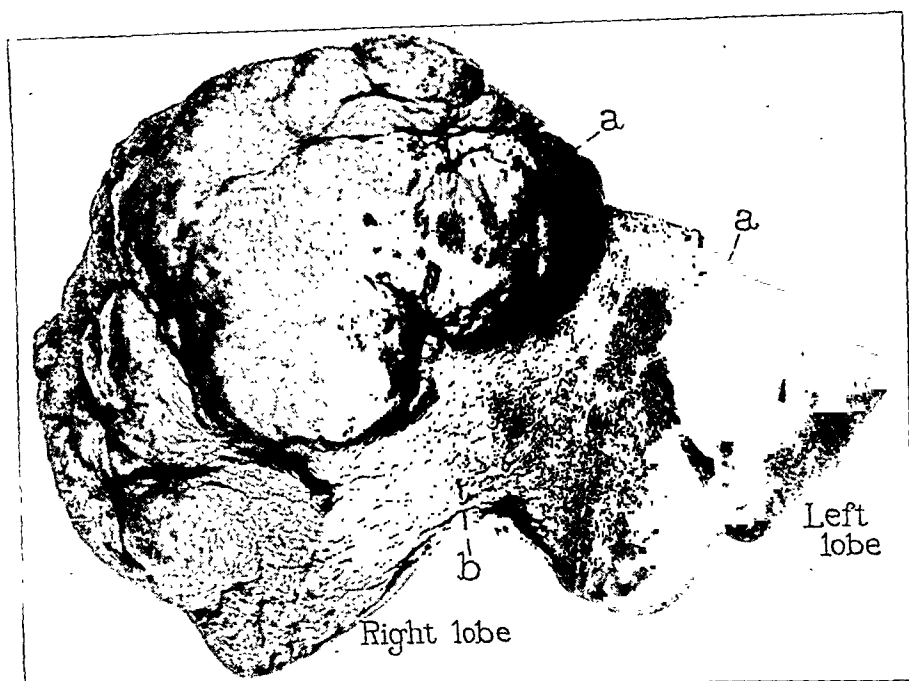


Fig. 4.—Chronic atrophy of the liver (toxic cirrhosis of large multinodular hyperplasia type); (a) large nodule of regenerated hepatic parenchyma; (b) “red atrophy”; this area is composed of shrunken hepatic stroma, in which there has been almost complete destruction of the hepatic parenchyma. Regenerative nodules are absent.

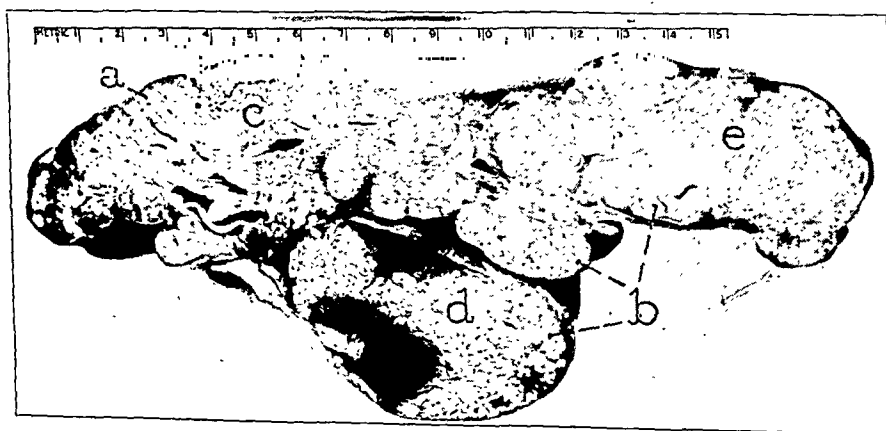


Fig. 5.—Chronic atrophy of the liver (toxic cirrhosis). Marked deformity of the organ due to irregularity of regeneration; (a) “red atrophy” without regeneration, consisting of contracted hepatic stroma; (b) regenerated nodules of parenchyma; (c) right lobe; (d) caudate lobe; (e) left lobe.

biosis, were seen (fig. 6). In the necrotic zones the cells stained faintly and appeared to be undergoing lysis. Polymorphonuclear and mononuclear phagocytic leukocytes pervaded the peripheral lobular zones and extended to some extent into the region occupied by the necrobiotic cells. Necrosis appeared to be more extensive in the central lobular regions than at the lobular periphery. In a few regions, either partial or complete clearing of the degenerated cells had been effected. Wherever this had occurred there remained a markedly congested sinusoidal bed, the

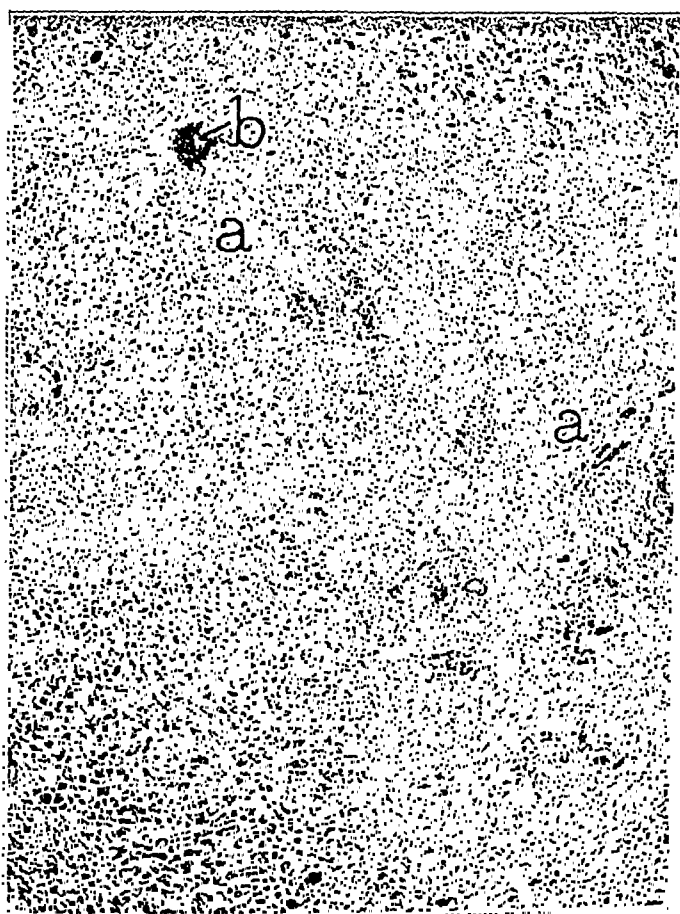


Fig. 6.—Acute atrophy of the liver, revealing extensive lobular necrosis and disorganization; (a) where the cellular detritus has been cleared, the sinusoids and reticulum are prominent; (b) or congested; prominent periportal bile ducts are seen in the middle right portion. Hematoxylin and eosin; $\times 65$.

original reticulum of the lobule having been dismantled and appearing as a bare connective tissue framework.

In the subacute stage the markedly disorganized state of the liver, owing to the preceding necrosis of hepatic cells, was prominent (fig. 7). The picture presented by this disorganization varied in different microscopic fields in the same case and in the various cases of the group. Small clusters of hepatic cells were sometimes seen surrounding the

periportal connective tissue. In other regions, the hepatic cells appeared singly or were arranged in a partially intact hepatic cord, whereas in still other cases or other regions of the same case, nearly intact lobules could be found, but usually with dismantled portions about the central vein or with bands of lobular dismantling existing between the portal and central veins. In a few cases it appeared as though the necrosis was progressive, but usually it was either ended or so mild and slowly progressive that its presence was not distinguishable by histologic methods. The disappearance of the hepatic parenchyma left the peri-

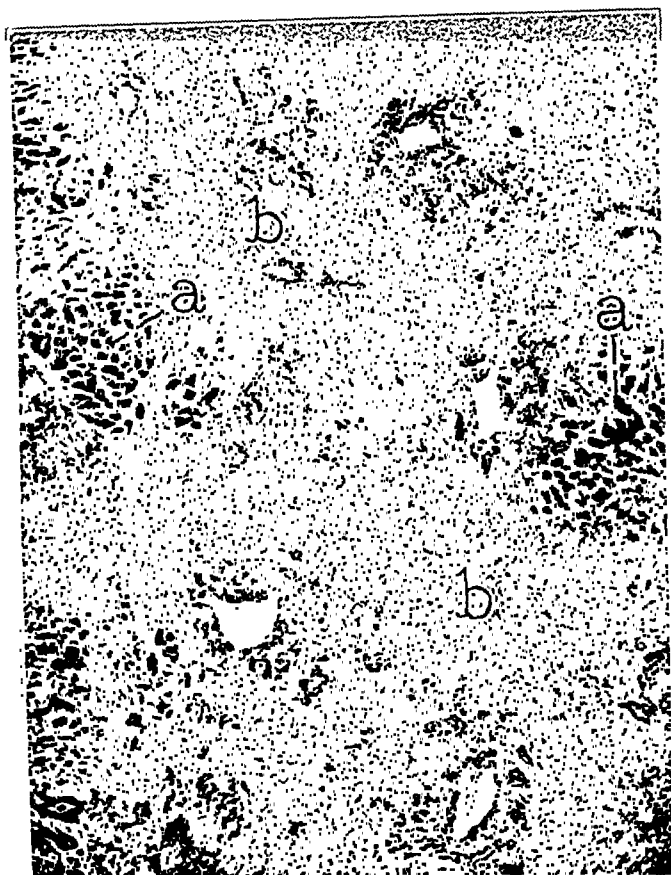


Fig. 7.—Subacute atrophy of the liver; (a) the isolated group of hepatic cells, nestled at one side of the intralobular zones. The detritus of the necrotic hepatic cells has been cleared at (b) leaving the framework of the liver very conspicuous (grossly red areas). Bile ducts are prominent in the periportal zones owing to the loss of surrounding hepatic cells. Hematoxylin and eosin; $\times 75$.

portal biliary ductal structures dismantled, so that they were very prominent. Although in some instances the number of bile ducts appeared to be increased, it was not possible definitely to ascertain that the increase was due to actual ductal proliferation. The appearance of intralobular proliferation of bile ducts, in many instances at least,

resulted from the retrogression of hepatic cords, which seemed sometimes to assume tubelike formation.

In the older cases of subacute atrophy there was evidence of regeneration of hepatic parenchyma beginning from the better preserved groups of hepatic cells (fig. 8). Regeneration, however, was never marked at this stage. In places where lobular dismantling had occurred, the connective tissue was composed of the original hepatic stromal substances, somewhat contracted but still arranged so that lobular identi-



Fig. 8.—Subacute atrophy of the liver. Group of regenerating hepatic cells in an intermediate lobular position, apparently cut off on either side; (a) both periportal and central lobular zones are dismantled; in the dismantled areas congested sinusoids are prominent. Bile ducts are conspicuous in the periportal zone (lower left). Hematoxylin and eosin; $\times 100$.

fication was possible. The sinusoids of such skeletonized lobules were frequently congested, but sometimes there had been sufficient stromal contraction to occlude them. Lymphocytes and other mononuclear leukocytes were collected beneath Glisson's capsule and in the periportal connective tissue; these, however, were never numerous. Interference with the flow of bile frequently resulted in the formation of bile thrombi in the biliary canaliculi of the hepatic cords or in the intralobular tube-

like structures. Lipoids were frequently observed in the hepatic cells that remained in group formation but more especially in the retrogressive isolated hepatic cells, miniature cords or intralobular tubelike structures.

In the chronic stage evidence of retrogression was rarely to be observed in the hepatic cells, but, on the contrary, regeneration prevailed (fig. 9). This was most evident in the cases of the late chronic group, but its gradual evolution, beginning in the late subacute stage and progressing throughout the chronic series, was apparent. Regeneration

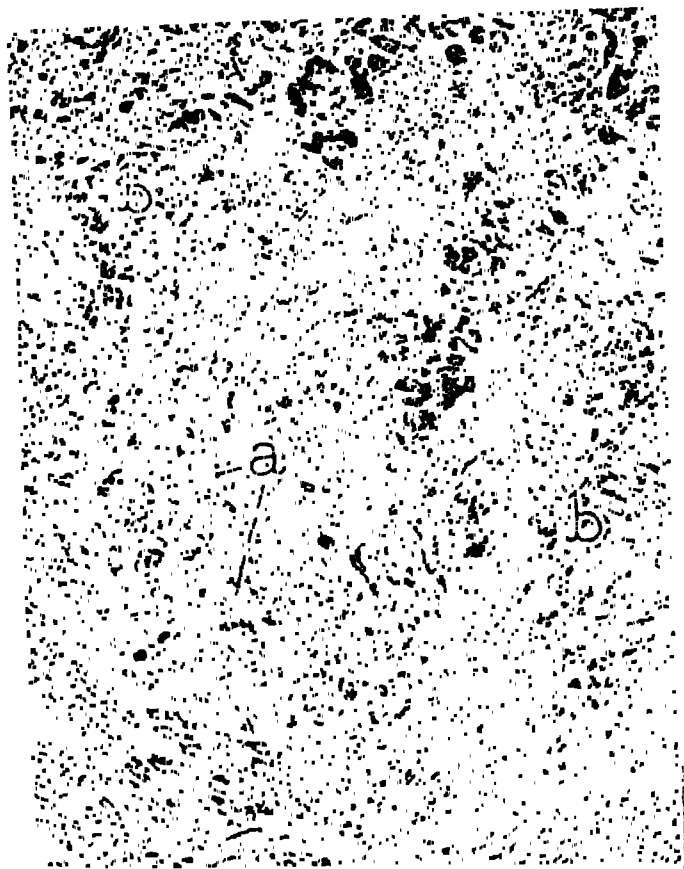


Fig. 9.—Chronic atrophy of the liver (early toxic cirrhosis); (a) structures resembling tubules are prominently displayed about the periphery of the lobules; (b) nodules of regenerating hepatic cells; the hepatic stroma is shrunken, with sequential narrowing of the sinusoidal bed. Hematoxylin and eosin; $\times 65$.

usually proceeded from the better preserved groups of hepatic cells, and appeared to occur by a process of hypertrophy and hyperplasia of the cells, although the actual evidences of cellular growth were difficult to find. The regeneration occasionally appeared to come also from the hepatic cells of the small, previously mentioned, intralobular, tubelike structures. Regeneration by this means, however, was exceptional.

The regenerating lobules formed as nodules of hepatic parenchyma. The hepatic stroma appeared to be contracted by the nodular growth. There was no evidence that it was invaded by the growth. The connective tissue became progressively shrunken, in the cases of longer duration, until a dense connective tissue was revealed, usually, though, with identification of the skeletonized lobule still possible. This contraction was accentuated where the stroma was impinged on by growing nodules of parenchyma (fig. 10). As shrinkage of the connective tissue



Fig. 10.—Chronic atrophy of the liver; late stage of toxic cirrhosis. The hepatic stroma is compressed by regenerated lobules of varying size in nodular formation. Van Gieson stain; $\times 35$.

advanced, the formerly patulous sinusoids were closed, and periportal biliary ducts and intralobular tubelike structures appeared to atrophy with it. Lymphocytic collections in the periportal connective tissue and in the skeletonized lobules were rarely abundant. In the cases of subacute and chronic atrophy, although the clinical termination of the disease usually suggested an exacerbative hepatic change, this appearance was never confirmed in the histologic studies of the liver. Evidences of fresh extensive necrosis of cells were never found.

Ascites and Jaundice.—This description would not be complete without suggested explanations of the development of ascites and jaundice in the presence of this lesion. Anatomic evidence points to the ascites as being due to portal obstruction caused by the closing down of the sinusoidal and intralobular venous circulation. Its early appearance, before changes in the better supported portal veins had occurred, suggests that it was not necessarily dependent on narrowing of the portal veins themselves. In later stages, however, hyaline changes, with thickening of the portal veins, indicate that eventually they too entered into the process of obstruction.

The presence of bile thrombi in the bile canaliculi gave the impression of obstruction to the flow of bile. This could be accounted for on the basis of disorganization, rupture or crowding of the hepatic cords. Obstruction due to cholangitis was never found. Much more important than obstruction, however, in the production of jaundice in these cases of hepatic atrophy was the diminution of hepatic parenchyma, which holds not only for the acute stages but for the subacute and chronic stages.

Anatomic Changes in Other Organs.—The initial toxic substances exerted but little effect on other organs than the liver. Degenerative changes occurred in them, probably because of metabolic toxins that accumulated as a result of the hepatic dysfunction.

The kidneys at the time of death were usually involved in an acute, diffuse, toxic type of degenerative change characterized by swelling and intensive bile staining. The bile pigment could be seen in the tubular epithelial cells and within tubules in the form of bile-stained casts. The epithelial cells of convoluted tubules and Henle's loops were swollen, granular and vacuolated, sometimes showing evidence of necrosis and desquamation, and usually containing fine droplets of fat. Glomeruli were apparently not involved. Sometimes, except for bile staining, the kidneys appeared to be normal. In the kidneys in one case, extreme fatty change with fat within tubular cells and the tubular lumens was observed.

The pancreas appeared to be normal in half of the cases. It showed evidences of chronic changes characterized by atrophy and interstitial pancreatitis in seven cases. In five cases there was an acute change characterized by fat necrosis and polymorphonuclear leukocytic exudation. This was never severe, but rather of focal type.

The spleen weighed 200 Gm. or more in only six cases, and in only two cases was the weight more than 300 Gm.; in one case the weight was 340 Gm., and in one it was 975 Gm.

Ascites was found in the early cases only occasionally, and was extremely mild; usually there was none. Its absence was apparently not connected with duration or the exact fibrotic state of the liver, for it was not present in two cases that were representative of the relatively late cirrhotic stages. In these cases, its absence was probably to a considerable extent dependent on development of collateral circulation, although at necropsy evidence of this was not clear.

The thyroid gland was examined in eleven cases, and in these it was normal, except for mild hyperplasia of epithelial cells in one case; in another case there was only a small fetal adenoma.

The heart muscle usually was the seat of a moderately severe fatty degenerative change. Usually small epicardial or subendocardial petechial hemorrhages were seen.

Hemorrhages, as represented by purpuric spots on the skin, or petechiae on the pleura, peri-endocardium, peritoneum, mucosa of the intestinal tract or in the mucosa of the genito-urinary tract, were almost constantly found.

In fifteen cases, passive congestion of the lungs existed, in four of which definite evidence of terminal bronchopneumonia was observed.

In the suprarenal glands there was anatomic evidence of pathologic change in only three cases. In two cases there were small zones of deposition of calcium in the medulla and in one case a small adenoma of the cortex.

None of the cases revealed the existence of old or previous hepatic disease. Previous changes could easily have been obscured by the atrophy, but old fibrosis resulting from injury should easily have been detected in the sections subjected to the van Gieson stain.

SUMMARY

Clinical and pathologic study of twenty-two cases of atrophy of the liver revealed a common pathogenesis but probable widely differing etiology. The lesion begins in relatively rapid atrophy of the liver, and, according to severity and rapidity of the atrophy and associated changes, may be revealed as an anatomically acute, subacute or chronic lesion. Progression into the chronic stage is dependent not only on a relatively less severe destruction of hepatic parenchyma, but on the capacity of the hepatic cells to regenerate. The clinical course of the disease is frequently impossible of pathologic correlation, owing to the somewhat latent appearance of the clinical manifestations; however, in a general way the disease exhibits gradations in symptomatic severity and duration similar to those suggested by the pathologic anatomy of

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the liver. The most constant symptom presented in these cases is jaundice. Ascites is somewhat latent in its development, but is usually shown when the lesion has reached chronicity. The occurrence of pain in the course of this disease, simulating colic originating in obstruction from biliary calculi, has been emphasized. By far the greater number of patients live to reach the clinically and anatomically sub-acute and early chronic stages. Death from acute hepatic atrophy, so far as pathologic anatomy reveals it to be acute, is exceedingly rare. In some cases, the end or healed stages of the lesion is reached; this stage presents the characteristics of the type of cirrhosis that Mallory has designated "toxic cirrhosis."

OSTEOGENIC SARCOMA

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(Concluded from page 659)

PART II: THE FIBRO-OSSEOUS FORMS OF OSTEOGENIC SARCOMA

Ossifying connective tissue is of two types, that which ossifies in the wake of calcified cartilage and that which forms bone of the membranous type independently and directly. While these two forms of ossification have long been recognized by embryologists, it is erroneous to assume that the formation of membranous bone is restricted to a few flat bones of the skull and that so-called intracartilaginous ossification (bone in the wake of the cartilage) is the uniform rule in the long bones. It is true that the cancellous portion of the long bones is produced by a more primitive ossification which is dependent on a previous storage of calcium in cartilage. But it is likewise true that in the appendicular skeleton a rim of compact cortical bone is formed directly by a more highly differentiated connective tissue after the perichondrium has been transformed into periosteum of the adult type, and this periosteum in its active portions retains throughout life the power to direct osseous formation.

In the osteogenic sarcomas of fibro-osseous origin it is necessary to distinguish between the form of sarcoma that is related to the function of production of cancellous bone, and is therefore clinically a central sarcoma of bone, and the form of osteogenic tumor that is related to the function of formation of cortical bone and is clinically a periosteal ossifying growth. The first form of neoplasm, which arises most frequently in the cancellous portions of the long bones, is osteolytic and a more primitive tumor than the periosteal sarcoma of the sclerosing type, which arises from the osteogenic layers of the periosteum.

THE OSTEOLYTIC FORM OF OSTEOGENIC SARCOMA

The osteolytic or earlier fibro-osseous form of osteogenic sarcoma is not frequently described as a separate entity, although it has long been recognized as a source of confusion in the diagnosis of tumors of the bone. In the older treatises on pathology, from the time of Virchow up until about 1910, this form of tumor was either referred to as a malignant cyst or aneurysm of the bone, or it was described histo-

logically as an angiosarcoma of the bone. The term "malignant bone aneurysm" can easily be understood if one is familiar with the gross pathologic process of these lesions, since this form of sarcoma is essentially a central destructive growth in which a mass of necrotic bone within the confines of a cortical shell is often replaced by hemorrhagic and vascular tissue. However, as far back as 1876, it was recognized that this was in all probability not a vascular lesion in the bone but a genuine neoplasm of osseous tissue. Sir James Paget,⁵ in his lectures on surgical pathology, in 1876, wrote in regard to aneurysms of the bone and the so-called osteo-aneurysms:

I am far from convinced that, in all the cases thus entitled, the blood vessels of the bone were primarily or chiefly diseased. My impression is that in many of them the disease was really medullary cancer or myeloid tumor of the bone with large development of vessels, and that in some it was such a blood cyst as appears to be sometimes formed in the course of a myeloid or cancerous disease.

Notwithstanding the early origin and the extent of the literature that has accumulated on this subject, this form of sarcoma is rarely recognized in the roentgenogram. Even with the benefit of microscopic examination, competent surgeons and pathologists are repeatedly diagnosing this lesion either as a form of osteitis fibrosa or of giant cell tumor. This mistake accounts for several reports of so-called metastatic giant cell tumors that have recently crept into the literature (Geschickter and Copeland²).

Clinical Features.—The clinical features of this osteolytic sarcoma are marked by a wide age distribution, the variability of the region of the bone involved and the frequency of pathologic fracture. The incidence of the disease is maximal, between the ages of 10 and 20, and falls away gradually in the latter decades, but may occur at any age throughout life (fig. 46). Like the other forms of osteogenic sarcoma, the disease is most prevalent in the long bones and most frequently affects the lower end of the femur and the upper end of the tibia. With the exception of pathologic fracture, which occurs in approximately 50 per cent of all cases, the symptomatology of this group of neoplasms is not unique. Trauma is given as the initial event in less than 25 per cent of the lesions, and the usual sequence of symptoms is pain, tumor, limp, trauma and fracture. The average duration of symptoms is slightly under one year prior to the initial treatment (table 4).

As in the other forms of sarcoma of the bone, evidence of a systemic reaction in the form of fever and leukocytosis may be observed at any time during the clinical course. The temperature may range between 99 and 102 F., and the leukocytosis from 11,500 to 17,000. The regional lymph nodes may be enlarged, and in one instance metastatic involvement was microscopically proved.

TABLE 4.—*Osteogenic, Osteolytic Sarcoma*

P. N.	Race, Sex and Age	Location	Duration, Mos.	Symptoms	Röntgen Findings	Treatment	Microscopic Findings	Result
42344	W F 20	Femur, lower	3	Pain, tumor six weeks	Destruction in condyle, translucent periosteal shadow	Amputation, September, 1929	Early osteolytic	Metastases to chest 6 mos. later
42344	W F 20	Femur, lower	3	Pain, tumor six weeks	Ossous destruction	Amputation	Mixed, spindle and round cells with giant cells	Dead
42014	(Monkey)	Radius, head	..	Pain, tumor	Resembling osteomyelitis	Incision and drainage, November, 1929; excision, November, 1929; curettement, December, 1929; curettement, May, 1930	Recurrence; well 2 mos. after last operation	
42014	(Monkey)	Radius, head	..	Pain, tumor	Resembling osteomyelitis	X-ray, April, 1928; Curettement, December, 1928; Curettement, March 9, 1927	Large spindle cells, pleomorphic osteoblasts	Dead Well 16 mos. after curettement
42418	W F 16	Tibia, upper	1½	Tumor	Osteolytic zone	Amputation	Large spindle cells, pleomorphic osteoblasts	Dead 1 yr. after operation
41504	W F 14	Ilium, right	2	Tenderness, limp	Subcortical, expanded	Amputation, March 24, 1917; amputation, Jan. 21, 1925	Large spindle cells, pleomorphic osteoblasts	Dead November, 1922
41104	W M 12	Tibia, upper left	12	Fluctuating tumor	lytic	Exploration, March 24, 1917; curettement, 1917; amputation, 1919	Mixed, round and spindle cells with giant cells	Lost
40913	W M 33	Humerus, upper	..	Pathologic fracture	Ossous destruction perforation of shell, some formation of bone	Curettement, 1921	Large spindle cells; pleomorphic osteoblasts; giant cells	Dead 3 mos. later; autopsy, general metastases
40768	W M 49	Femur, lower right	24	Pathologic fracture	Involvement of knee joint, for- mation; bone shell of tibia gone	Curettement, April 4, 1928; ampu- tation, June, 1928	Large spindle cells; pleomorphic osteoblasts; giant cells	Dead December, 1928
40768	W M 34	Tibia, upper left	12	Trauma, pain, swelling	Sclerosing periosteal	Excision of gland, March, 1928	Dead 7 mos. later
40768	W M 34	Tibia, upper left	12	Trauma, swelling, pain	Sclerosing periosteal	Excision of gland, March, 1928	Dead 7 mos. later
40226	W M 12	Tibia, mid- portion	5	Pain, tenderness	Mottled slight destruction	Operation advised against	Malignant spindle cells, a few osteoblasts	Dead 70 days later
40440	W M ..	Humerus, upper	7	Pain since Sep- tember, 1926, limp	Mottled slight destruction	Amputation, Sept. 30, 1927	Large spindle cells, pleomorphic osteo- blasts	Dead 2½ yrs. later
39970	W M 35	Femur, upper	6	Pain, tumor	Ossous destruction, soft part shadow	Amputation, June 3, 1927	Large spindle cells, pleomorphic osteo- blasts, many giant cells	Dead 2½ yrs. later
39970	W M 35	Femur, upper	6	Pain, tumor	Ossous destruction of bone; little formation of shadow, large soft part shadow, metastases to chest (?)	Biopsy, May, 1927	Large spindle cells, pleomorphic osteo- blasts, many giant cells	Dead 2½ yrs. later
39970	W M 35	Femur, upper	6	Pain, tumor	Ossous destruction of bone; little formation of shadow, large soft part shadow, metastases to chest (?)	Biopsy, May, 1927	Large spindle cells, pleomorphic osteo- blasts, many giant cells	Dead 2½ yrs. later
39970	W M 35	Femur, upper	6	Pain, tumor	Ossous destruction of bone; little formation of shadow, large soft part shadow, metastases to chest (?)	Biopsy, May, 1927	Large spindle cells, pleomorphic osteo- blasts, many giant cells	Dead 2½ yrs. later
39251	W F 15	Femur, lower left	1½	Pain, trauma	Ossous destruction of bone angle formation of bone

Dead 6 wks. after examination
Well 29 mos. later

Dead 5 mos. later

Malignant spindle cells, a few osteoblasts; a few giant cells

Malignant spindle cells, Lost

Malignant spindle cells, Dead 5 mos. later

Malignant spindle cells, Well 9 mos. later

Many malignant spindle cells, a few pleomorphic osteoblasts

Recurrence after curettement; ampu 11 mos. after amputation

Malignant spindle cells, a few osteoblasts

Well June, 1930

Malignant spindle cells; Malignant spindle osteoblasts

Dead

Malignant spindle cells, Well 3 yrs., now dead

Pleomorphic osteoblasts

Malignant spindle cells and pleomorphic osteoblasts

Dead 5 mos. later

Malignant spindle cells, pleomorphic osteoblasts, osteoid tissue

Dead 1 yr. later

Dead 1 yr. later

Dead 4 mos. later

Dying with metastases, Sept. 12, 1924

Well 1 yr., 4 mos., lost

Mixed, spindle and round cells

Malignant spindle cells, later

Dead 1 yr., 2 mos.

Malignant spindle cells, pleomorphic osteoblasts, much osteoid material

Dead 4 mos. later

Dead 1 yr., 3 mos. later

Resection, June, 1927

Amputation, Feb. 2, 1927

Amputation, July 24, 1926

Amputation, July, 1926

Amputation, July 14, 1926

Amputation, March 25, 1927; curettement, Jan. 25, 1926

Amputation advised

Exploration 4 times in two months, amputation, Aug. 30, 1925

Exploration, 1924; amputation advised, 1925

Properative radiation; amputation, April 24, 1925

Amputation

Exploration, April 21, 1924; amputation, May 10, 1924

X-ray, December, 1, 1922

Amputation, Dec. 1, 1922

Amputation, June 2, 1923

Amputation, Dec. 13, 1923

Amputation, Nov. 23, 1923

Curettement, August, 1923

X-ray; amputation, Sept. 11, 1923; amputation, Sept. 23, 1923

Exploration, Sept. 23, 1923

Much osseous destruction, right angle formation of bone

Osseous destruction of bone; angle part shadow, form

Osseous destruction, periosteal reaction of bone, roughened cortex

Central destruction, formation of bone

Osseous destruction

Pathologic fracture, excess callosus

Periosteal reaction and destruction, soft part and expansion

Osseous destruction with cystic areas and expansion

Osseous formation with expansion involving bone

Destruction, periosteal roughening

Mottled-periosteal lipping

Osteoporosis, formation of bone

Osteoporosis and destruction

Central destruction, onion-peel periosteal appearance

Destruction, raised periosteum

Trauma, pain, tumor

Trauma, pain, tumor

Trauma, pain, tumor

Trauma, pain, tumor

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Trauma, pain, tumor

4 Osteogenic, Osteolytic Sarcoma—Continued

P.N.		Race, Sex and Age	Location	Duration, Mos.	Symptoms	Roentgen Findings	Treatment
33512	W M 11		Femur, lower right	1	Trauma, pain, pathologic fracture	Exploration, Feb. 4, 1923; irradiation, April 23, 1923; amputation, May, 1923
						Resembling giant cell tumor	Amputation, December, 1921
32908	W F ..		Femur, lower	Exploration, Dec. 6, 1922; amputation, April, 17, 1922
32663	W M 20		Humerus, upper	4	Pain, trauma, fracture	Incision, Nov. 19, 1922; amputation, Dec. 13, 1922
32278	W M 30		Humerus, lower	1	Trauma, pain, tumor	Destruction, roughened periosteum	Curettement, June, 1920; amputation, July, 1920
32053*	W M 14		Tibia, upper right	1	Trauma, pain, tumor	Curettement, 1908; amputation, 1909
31890	W M 35		Tibia, lower	7	Pain, tumor	Central destruction	Curettement, 1908; amputation, 1909
31695	W F 16		Femur, mid-part	1 1/2	Pain, swelling	Osseous destruction with roughened periosteum	Curettement, August, 1922; irradiation; amputation, Jan. 6, 1923
31383	W F 16		Femur, lower shaft	5	Pain, tumor	Excision, Aug. 4, 1921; amputation, Aug. 5, 1921
30180	O F 20		Tibia, mid-part	3	Swelling, pain, pathologic fracture	Diffuse destruction, some osseous formation	Exploration, Jan. 6, 1922; amputation, Jan. 10, 1922
29400	W M 32		Femur, lower left	16	Pain, tumor	Destruction of bone shell	Excision, Feb. 4, 1921; curettement, March 5, 1921; amputation, April 30, 1921
29363	W M 21		Femur, lower right	4	Trauma, pain, swelling	Great destruction	Amputation, July 12, 1921
29362	W F 67		Femur, lower right	6	Pain, swelling, pathologic fracture	Destruction of ischial ramus	Curettement, March 21
29361	W M 27		Ischium	24	Trauma, swelling	Osseous destruction and onion-peel formation	Exploration, Oct. 29, 1921; amputation, June, October, 1921, August, 1921
29084	W M 56		Femur, upper left	4	Pain	Amputation, March 17, 1921
28925	W F 14		Tibia, upper	2	Pain, tumor	Extensive destruction	Amputation, March 17, 1921
				12	Pain, tumor, fracture

Dead 3 yrs. after amputation

Lost

Malignant spindle cells, pleomorphic osteoblasts

Dead 2 mos. after operation

Dead 1 yr., 7 mos. later

Dead 3 mos. after amputation

Dead same year

Alive 3 yrs. after operation, lost

Dead 4 mos. later

Well nearly 9 yrs. after amputation

Well 18 yrs., 4 mos. later

Dead

Dead July 16, 1921 from other causes

Dead 6 mos. later

Dead 3 yrs., 5 mos. later

Dead 3 mos. later

Dead 2 mos. later

Dead 2 mos. later

Dead 2 mos. later

Dead 2 mos. later

Curettement, Nov. 26, 1917; irradiation, Oct. 17, 1918

Exploration, Coley's toxins

Amputation, 1917

Excision, February, 1921

Amputation, April 8, 1921

Amputation, Feb. 4, 1921

Exploration, March 18, 1921; preoperative irradiation, July 1921

Toxins, preoperative irradiation of pelvic region and glands, amputation arm; excision, June 22, 1921

Resection, June 5, 1901; amputation, June 7, 1901

Amputation, August, 1920

Exploration, January, 1917; followed by Neisser's serum; amputation, August, 1920

Dec. 22, 1920 September, 1920; Curettement, October, 1920

Amputation, June 22, 1909; excision, July 4, 1909; amputation, Aug. 5, 1909

None

Two amputations

Amputation, Aug. 25, 1919

Preoperative irradiation, May 5, 1918; amputation, June 6, 1918

Amputation and Coley's toxin, July 3, 1918

Amputation, Feb. 9, 1915

Central lesion

Destruction of acetabulum, head and neck of femur

Central osseous destruction, slight formation of bone

periosteal reaction

Skull defect in frontal bone

Central tumor with expansion and periosteal reaction

Central tumor with expansion and periosteal reaction

Marked osseous bone destruction with pathologic fracture, tumor of soft part and slight formation of bone, cortical expansion

Pathologic fracture

Pathologic fracture

Pathologic fracture

Pathologic fracture

Pathologic fracture

Pathologic fracture

Pathologic fracture

Pathologic fracture

Pathologic fracture

Pathologic fracture

Pathologic fracture

Definite trauma

Fracture, December, 1919

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

Pain, tumor

26577 W M 20 Tibia, right

26578 W M 20 Femur, head

26579 W M 20 Tibia, upper

26580 W M 20 Tibia, right

26581 W M 20 Tibia, right

26582 W M 20 Tibia, right

26583 W M 20 Tibia, right

26584 W M 20 Tibia, right

26585 W M 20 Tibia, right

26586 W M 20 Tibia, right

26587 W M 20 Tibia, right

26588 W M 20 Tibia, right

26589 W M 20 Tibia, right

26590 W M 20 Tibia, right

26591 W M 20 Tibia, right

26592 W M 20 Tibia, right

26593 W M 20 Tibia, right

26594 W M 20 Tibia, right

26595 W M 20 Tibia, right

TABLE 4.—*Osteogenic, Osteolytic Sarcoma—Continued*

P. N.	Race, Sex and Age	Location	Dura- tion, Mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Result
16571	W M 21	Femur, midpart	2	Trauma, pain, tumor	Exploration, Nov. 19, 1914; ampu- tation, Dec. 2, 1914	Malignant spindle cells, pleomorphic osteo- blasts; giant cells	Dead 5½ mos. later
16158	W M 16	Tibia, upper	2	Tumor	Osseous destruction, periost- eal roughening	Exploration, Jan. 8, 1913; excision, upper third of tibia, Jan. 13, 1913; amputation at thigh, August, 1914	Mixed spindle cells, pleomorphic osteo- blasts with giant cells	Dead 1 yr. later
15404½	W F 18	Tibia	4	Trauma with re- paired fracture	Incision; amputation, Jan. 14, 1914	Malignant spindle cells, pleomorphic osteo- blasts	Dead from operation
14229	W F 35	Femur, lower	Central destruction (aneurysm)	Amputation, June 2, 1913	Mixed spindle and round cells, pleo- morphic osteoblasts, giant cells	Dead 11 yrs. later
13092	W M 39	Tibia, upper	24	Trauma, pain, tumor	Central destruction	Curettement, Aug. 8, 1912; toxins and amputation, Sept. 19, 1912	Mixed spindle and round cells	Dead 7 mos. later
12050	W M 26	Femur, lower	5	Pain, tumor	Exploration, Jan. 7, 1911; ampu- tation, Sept. 29, 1911	Mixed spindle and round cells	Dead 8 days after amputation, (toxemia)
11252	W M 60	Humerus, upper	17	Tumor, patho- logic fracture, trauma, pain	Amputation, July 25, 1911	Mixed spindle and round cells	Dead 6 mos. later
10868	W F 12	Femur, lower	2	Pain, swelling	Coley's toxin; curettement, Sept. 27, 1910	Large round cells	Dead 4 mos. later
10602	W M 30	Humerus, shaft	24	Pain, trauma, pathologic fracture	Central destruction	Curettement, Aug. 23, 1910; curette- ment, Oct. 10, 1910; amputation, April, 1912	Mixed spindle and round cells, osteoid substance, giant cells	Dead 4½ yrs. later amputation
9725	W F 12	Femur, lower	Amputation, May 31, 1909	Malignant spindle cells, pleomorphic osteo- blasts, a few giant cells	Dead 2 yrs. later
9397	W M 15	Tibia, head and shaft	2	Pain, tumor	Curettement; amputation, 10 days later	Mixed spindle and round cells	Dead 3 mos. later
9073	W M 24	Ulna, upper	20	Tumor	Resection, May 13, 1907	Spindle cells, giant cells	Dead 2 yrs. later
8182	W M 41	Femur, upper left	18	Limp, tumor	Osseous destruction	Exploration, May 8, 1907	Lost
7964	W F 17	Fibula, upper	9	Pathologic frac- ture, tumor, pain	Complete destruction	Amputation, 1904	Malignant spindle cells, pleomorphic osteo- blasts with giant cells	Dead 9 mos. later
6430	C M 13	Femur, lower	..	Pain, tumor	Exploration, May 29, 1905; ampu- tation, July 6, 1905	Malignant spindle cells, pleomorphic osteo- blasts	Lost
3350	W F 48	Tibia, upper	24	Pain, tumor	Exploration; amputation, 1901	Malignant spindle cells, pleomorphic osteo- blasts, giant cells	Well 2 yrs., lost
3231	W M 39	Tibia, upper	11	Pain, tumor, pathologic fracture	Amputation, Aug. 10, 1900	Malignant spindle cells, pleomorphic osteo- blasts, with giant cells	Dead 2½ mos. later
2181	W F 16	Tibia, upper right	5	Pain, tumor, repaired fracture	Exploration and amputation, 1899	Mixed spindle and round cells with giant cells	Dead 6 mos. later (pulmonary metas- tases and recurrence in stomach)
313	W M 22	Femur, lower	7	Pain, tumor	Osseous destruction	Exploration, Feb., 1890; amputa- tion, May, 1890	Mixed round and spindle cells	Dead 5 mos. after amputation

The usual point of origin of these growths is in the subcortical region of the metaphysis. The lesion, however, rapidly invades cancellous bone and the medullary spaces so that when examination is delayed the diseased area extends to a more central location, and the epiphysis or the shaft is involved. Once the new growth has reached the epiphysis, destruction of the bone is sufficiently advanced to create the typical vascular cavity suggestive of an aneurysm of the bone, and pulsation with symptoms referable to the joint may occur.

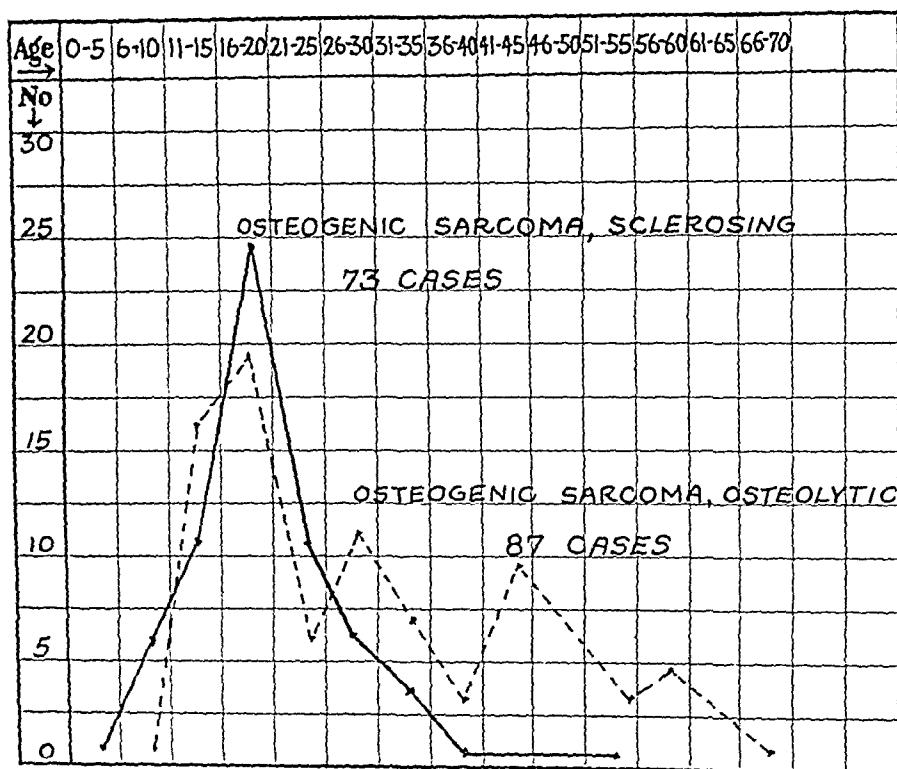


Fig. 46.—Chart showing the comparative age distribution of osteolytic (dotted line) and sclerosing (solid line) osteogenic sarcoma.

Examination of the affected limb reveals a swelling over which the skin is movable but tense, without much reddening (figs. 47, 48, 49 and 50). The superficial veins may or may not be dilated, depending on the size of the growth. On palpation, the peculiarity of these tumors is their boggy feeling and the slight suggestion of a semifluctuant nature. Pulsation, when present, immediately brings to mind the old clinical entity of the malignant aneurysm of the bone. Limitation may occur in the adjacent joint, but excess fluid in the joint cavity or actual involvement of the joint rarely occurs. In half of these cases an ununited pathologic fracture is present.



Figs. 47-50 (P. N. 39278).—A case of osteolytic sarcoma of the upper end of the humerus occurring in a white man, aged 22, who died two months after a primary amputation. This figure (fig. 47) shows the large boggy swelling over the upper end of the humerus characteristic of this type of neoplasm referred to in the old literature as malignant aneurysm of the bone.

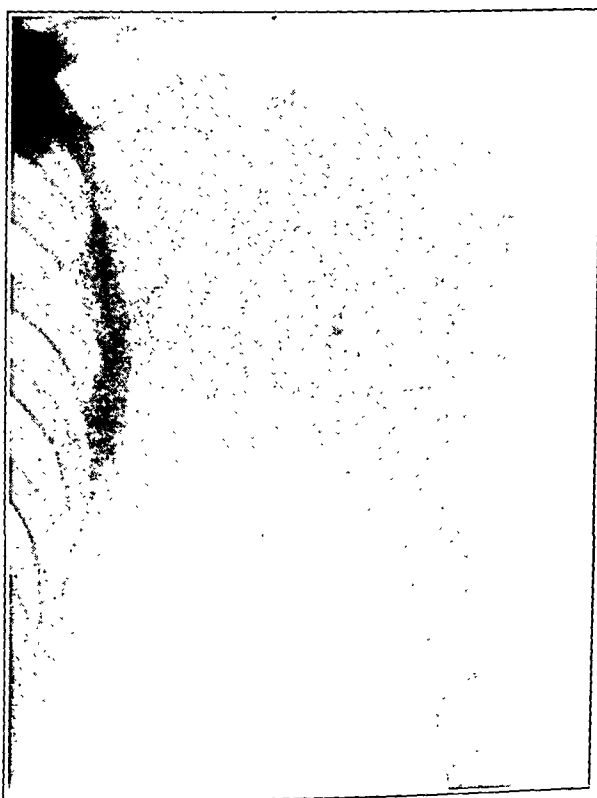


Fig. 48 (P. N. 39278).—Roentgenogram of the lesion. The upper end of the humerus has been replaced by a hemorrhagic mass of neoplastic tissue which has infiltrated into the soft parts.

Roentgenologic Features.—The x-ray films of this osteolytic form of sarcoma of the bone are extremely difficult to interpret. These lesions are confused with benign cyst of the bone, benign giant cell tumor, metastatic carcinoma to bone and Ewing's sarcoma, even by those experienced in roentgenologic diagnosis of lesions of the bone. Among those less experienced, the mistake of confusing this tumor with osteomyelitis is frequent.



Fig. 49 (P. N. 39278).—Gross specimen showing the hemorrhagic character of the neoplasm and its bone-destructive tendencies.

The most important diagnostic feature in the roentgenograms is the central area of irregular destruction of the bone which extends through the unexpanded cortex, resulting in a periosteal reaction. The early and late manifestations of the disease present different diagnostic problems from the roentgen standpoint.

In the early cases (figs. 51, 52, 53 and 55) the area of osseous destruction is subcortical and metaphyseal and slightly expands the overlying shell of cortical bone, thinning it and causing perforation or a melting away in one or more directions. The youthful age of the

patient, the osteolytic, central and metaphyseal character of the lesion immediately suggest the possibility of a benign cyst of the bone. The distinguishing features in the x-ray film, however, are the melting away and perforation of the bone shell at an early stage in the history of the disease at the time when the area of destruction is still asymmetrically located, the presence of a periosteal reaction and the slight degree of cortical expansion. In the benign cyst of the bone the bone shell

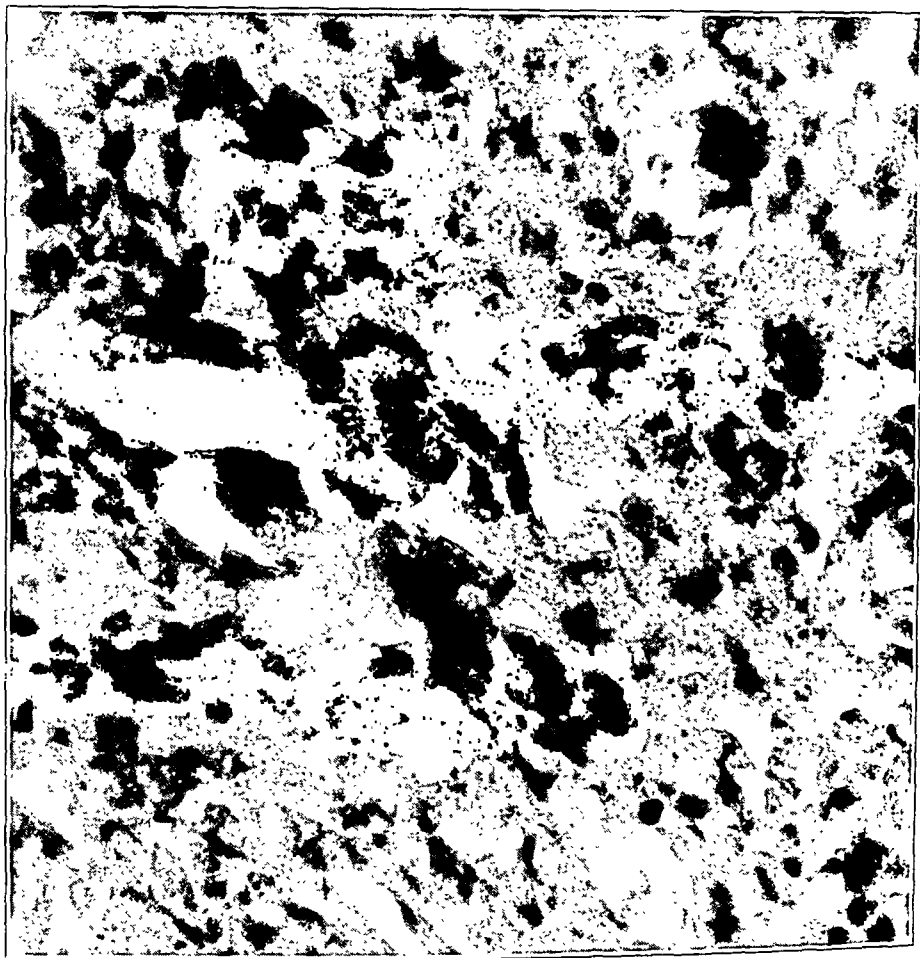


Fig. 50 (P. N. 39278).—High power photomicrograph of the tissue which is a mixture of malignant spindle and abortive osteoblasts. The large pleomorphic tumor cells are undergoing necrosis.

is symmetrically expanded, and the area of osseous destruction traverses the whole diameter of the marrow cavity before a pathologic fracture leads to perforation of the bone shell. There is also, in most instances, definite indication of the formation of new bone on the inner border of the expanded cortex, a finding lacking in osteolytic sarcoma (fig. 52).

In advanced cases, the marked osseous destruction and periosteal involvement make the diagnosis of malignancy relatively certain.

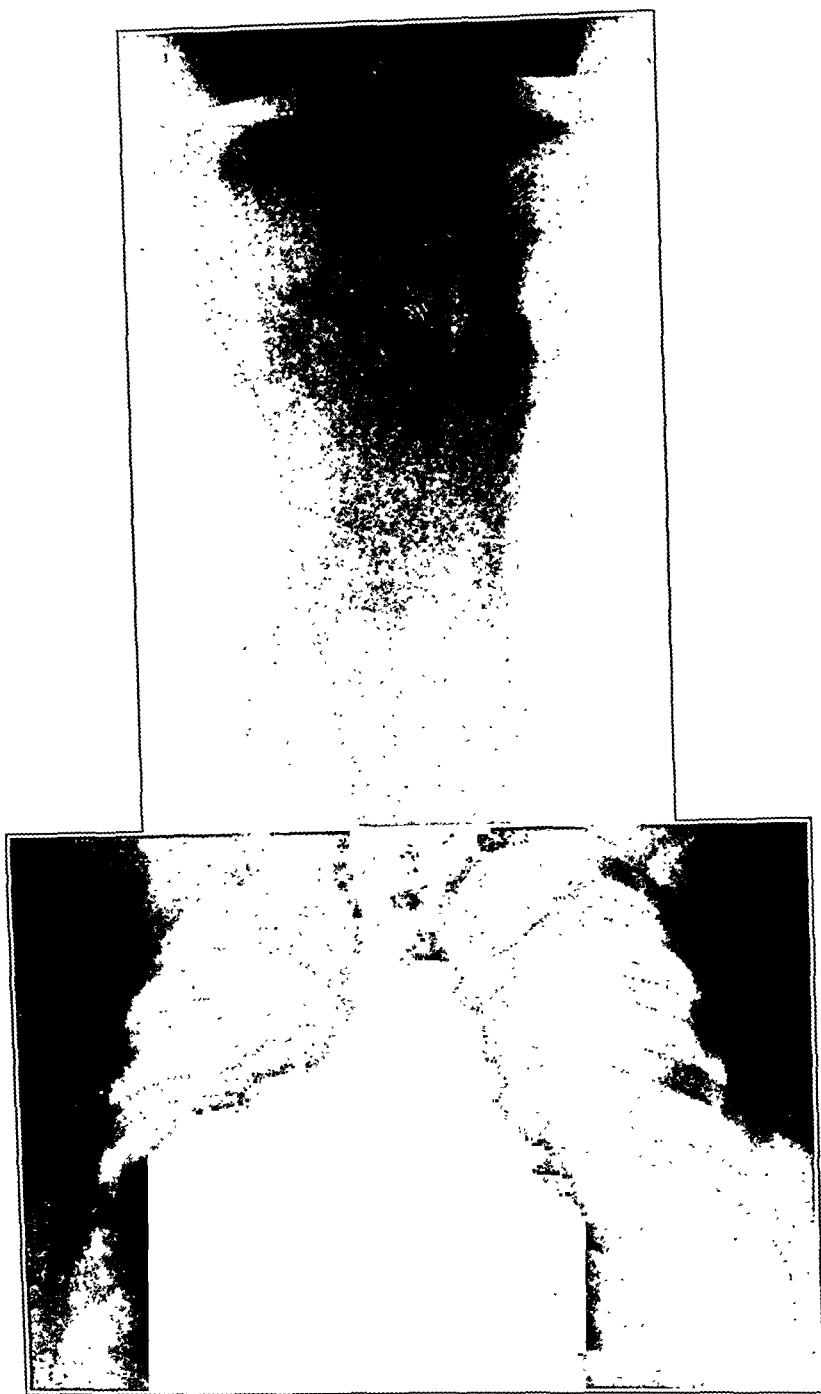


Fig. 51 (P. N. 16158).—Early roentgenogram of a case of osteolytic sarcoma in the upper end of the tibia of a white boy, aged 16, taken two months after the onset of symptoms. The tumor was three times excised before amputation was performed. The patient died one year afterward. A small area of osseous destruction is shown in a subcortical and metaphyseal location perforating the cortex. The roentgenogram of the chest taken shortly before death shows a huge mediastinal mass on the right, overlapping the heart shadow.

Metastatic carcinoma or a focus of multiple myeloma may then be suspected, but the bone has a more splintered and worm-eaten appearance and the degree of invasion into the soft part is far more pronounced in osteolytic sarcoma. Usually the youth of the patient will aid in making the distinction, since carcinoma and multiple myeloma are practically restricted to the years beyond 35, but it must be remembered that this form of sarcoma may also occur in later life.

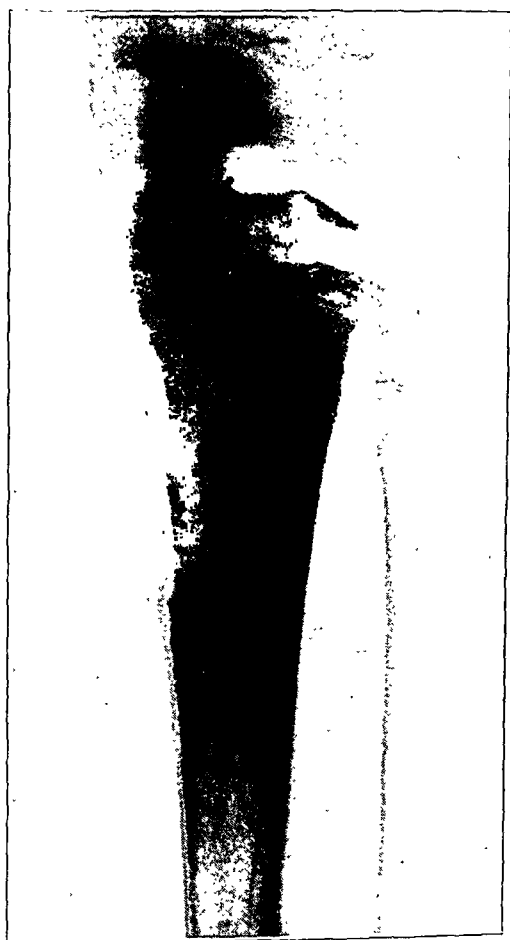


Fig. 52 (P. N. 41194).—Roentgenogram of an osteolytic sarcoma erroneously diagnosed as a cyst of the bone. The periosteal reaction, the perforation of the bone shell and the absence of osseous expansion led to the correct diagnosis from the roentgenogram in this laboratory.

The more protracted cases of osteolytic sarcoma are puzzling. These occur in adults and are nearly always confused with a benign giant cell tumor. The epiphysis is secondarily invaded by an expansile tumor with a perforated bone shell and a definite periosteal reaction (fig. 57). The metaphyseal portion of the bone is included in the tumorous process, and in several instances the joint cavity has become secondarily involved due to erosion or splitting of the articular cartilage. The history given

by the patient may extend over a period of from three to six years, and an operation, including exploration and biopsy, is necessary to rule out a benign giant cell growth. Cases of this type have been reported by Goforth,²⁸ Finch and Gleave,²⁹ Chatterton and Flagstad,³⁰ and others as metastatic giant cell tumor when the patients ultimately succumbed to metastases. A similar case recorded by Bloodgood³¹ as an authentic cure by amputation in this type of sarcoma has been classified by mem-



Fig. 53 (P. N. 41194).—Lateral view of the tumor shown in figure 52. This view emphasizes the similarity of the roentgenogram to a benign cyst of the bone.

bers of the Bone Registry as giant cell tumor, and its malignant nature doubted (figs. 58 and 59).

28. Goforth, J. L.: Giant Cell Tumor of Bone, *Arch. Surg.* **13**:846 (Dec.) 1926.

29. Finch, E. F., and Gleave, H. H.: A Case of Osteoclastoma with Pulmonary Metastases, *J. Path. & Bact.* **29**:399, 1926.

30. Chatterton, C. C., and Flagstad, A. E.: *J. Bone & Joint Surg.* **9**:113, 1927.

31. Bloodgood, J. C.: The Diagnosis and Treatment of Benign and Malignant Tumors of Bone, *J. Radiology* **1**:147, 1920.

The final status of these growths rests on a microscopic analysis and will be discussed in more detail subsequently when the histogenesis of this osteolytic form of sarcoma is considered.

Gross Pathology.—At exploration, a vascular tumorous mass may be found in the soft parts confined by muscle and fascia only. More



Fig. 54 (P. N. 41194).—High power photomicrograph showing the extreme anaplastic properties of the tumor cell. Note the mitotic figure of the cell in the center of the field. (Same case shown in figures 52 and 53.)

commonly the tumor is beneath the periosteum with the bulk of the neoplastic tissue within a shell of cortical bone. Vascularity is the rule, and a mass resembling a blood clot or active hemorrhage may be

encountered (figs. 49 and 59). In one case (fig. 60) an exploratory incision, made under the impression that an abscess was present, released a severe hemorrhage which resulted in a marked anemia, and in most instances in which the operation opens up the medullary spaces of the cancellous bone profuse bleeding occurs.

The neoplastic mass is soft and friable and usually resembles the blood-stained tissue seen in giant cell tumor. More fibrous areas, white

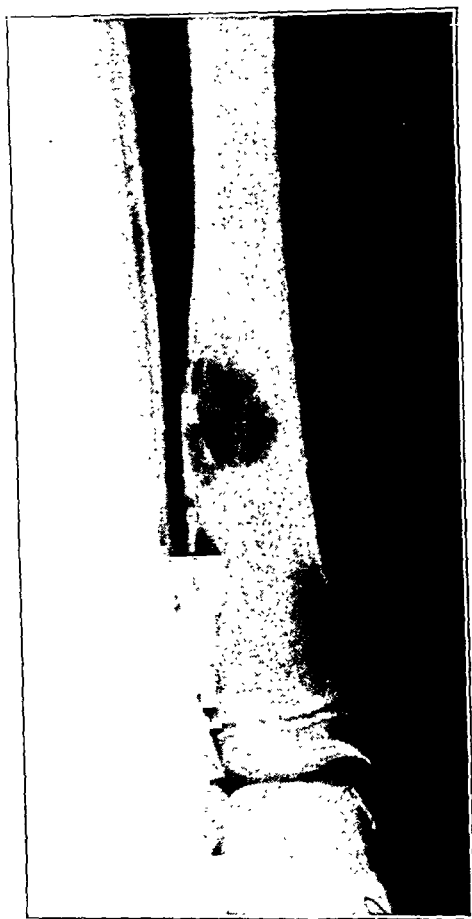


Fig. 55 (P. N. 36724).—An osteolytic sarcoma occurring in a boy aged 10, who died of metastases despite an early operation. The appearance in the roentgenogram is not unlike that of a cyst of the bone, except that the areas of destruction are asymmetrically located and have extended up and down the shaft of the bone rather than across the medullary cavity.

and firm, are usually to be found, and where this more consistent material predominates, secondary hemorrhagic cysts are enclosed by it.

Amputated specimens show a mixture of fibrous and hemorrhagic tumor tissue permeating the marrow cavity, rupturing the cortex and spreading subperiosteally and into the soft parts. The site of the tumor

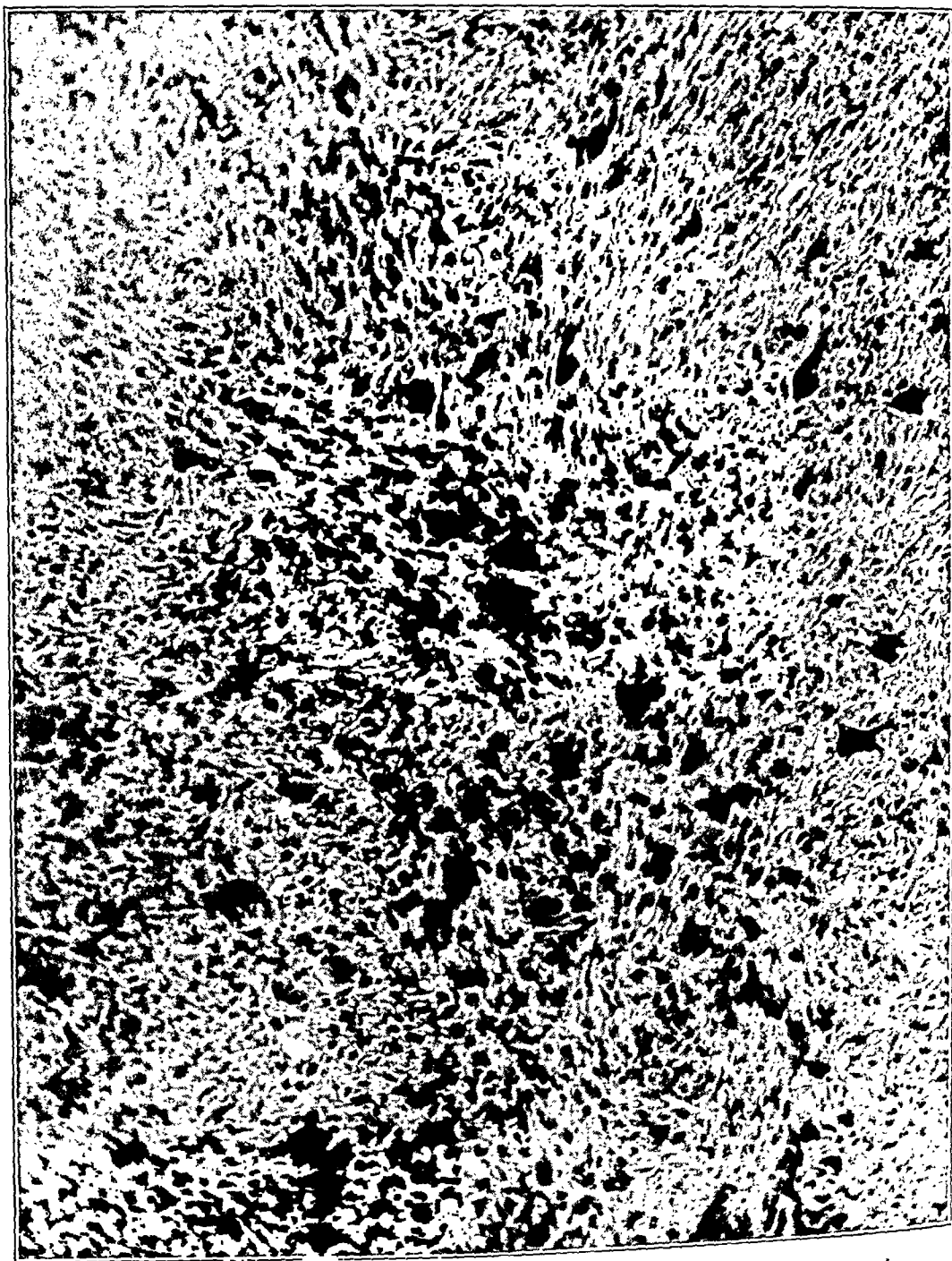


Fig. 56 (P. N. 36724).—Photomicrograph of lesion shown in figure 55, showing early osteoblasts and metaphyseal location and a definite periosteal reaction.

is practically always to the shaft side of the epiphysis, and at this point the shaft is usually fractured transversely. In early cases the cancellous bone in the medullary cavity is rapidly destroyed, and the cortex perforated at one or two points rather than melted away. This destruction in the medullary cavity seems to proceed rapidly until the cortex is ruptured and the pressure within the bone shell relieved, after which the tumor proliferates into the less resistant soft parts. However, with

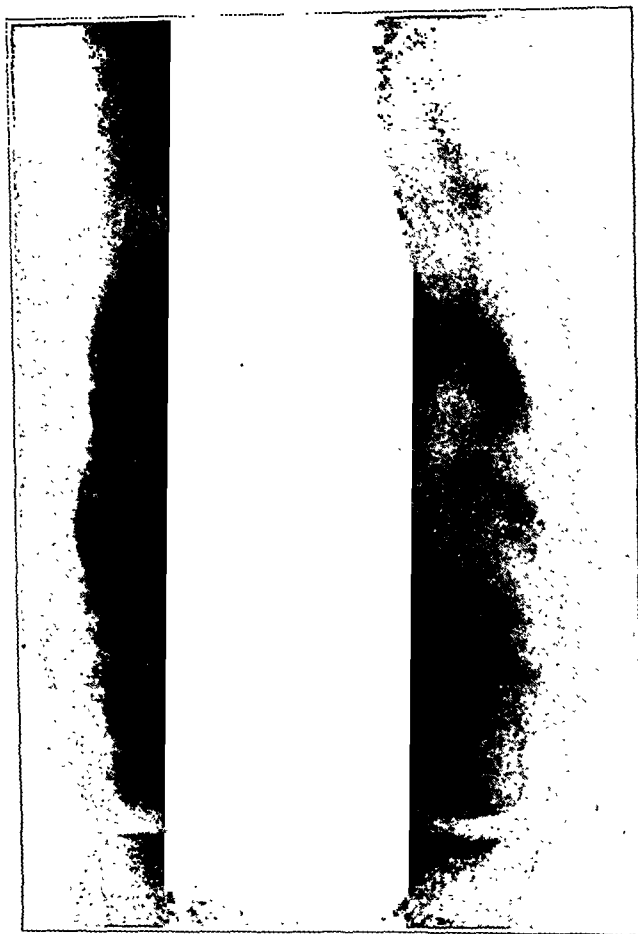


Fig. 57 (P. N. 40874).—A secondary osteolytic sarcoma reported by Chatterton and Flagstad (*J. Bone & Joint Surg.* 9:113 [Jan.] 1927) as a metastatic giant cell tumor, occurring in a white woman, aged 30, who died eight years after the initial symptoms with pulmonary metastases. The roentgenogram depicts the unusual amount of osseous expansion caused by the tumor, which has invaded the epiphysis.

the continued growth of the tumor, which now advances with less devastating effect under released pressure in the medullary cavity, the cancellous bone is capable of partial defense and reacts with slight sclerosis.

The central origin of the tumor, prior to its escape into the soft parts, is evident in the specimens by the fact that tumor perforates into the subperiosteal zones often in diametrically opposed directions. In advanced cases the entire shaft of the bone may be displaced with a white fibrous tumor tissue dotted here and there with hemorrhagic cysts (figs. 60 and 61).

Microscopic Features.—The microscopic sections account for the extreme vascularity of the tumor. Blood spaces usually without



Fig. 58 (P. N. 14229).—An osteolytic sarcoma arising secondarily in a woman, aged 61, who was cured by amputation. In the roentgenogram, the sarcoma was differentiated with difficulty from a benign giant cell tumor, but it has a more metaphyseal location and a definite periosteal reaction.

endothelial lining are prevalent in a tissue composed of plump malignant spindle cells and round abortive osteoblasts. One of the marked histologic features is the extreme degree of malignancy or anaplasia shown by the nuclei in cells of the various types. Hyperchromatism and mitotic figures are prominent throughout most of the sections (figs. 54 and 65). A varying amount of osteoid intercellular material can be

demonstrated. Often this preosseous material can be brought out only by special staining methods, but its definite tumorous origin is shown by its occurrence in metastatic pulmonary nodules.

Giant cells of the epulis type are common in the less rapidly growing neoplasms and are replaced by multinucleated tumor giant cells in the more malignant growths. The presence of these giant cells in the sections is often a source of confusion to pathologists, and explains why



Fig. 59 (P. N. 14229).—The gross specimen shown is characteristic of the old pathologic entity of malignant aneurysm of the bone. The microscopic structure of the tumor was typical of an osteolytic form of osteogenic sarcoma. (For roentgenogram see figure 58.)

some of the fatal cases of this form of osteolytic sarcoma have been reported as instances of metastasizing giant cell tumor.

The following are important points in the microscopic differential diagnosis: 1. In the absence of infection, the finding of the malignant plump spindle cells with dusty nuclei is pathognomonic of sarcoma when the specimen under examination has been taken from bone, and particularly when these dusty nuclei are duplicated within the same cell.

2. The large round cells with numerous mitotic figures referred to here as abortive osteoblasts are also characteristic of malignancy (figs. 65 and 66). These two malignant forms of spindle and round cells are common to osteolytic sarcoma in bone and are never found in an uninfected benign giant cell tumor. The benign giant cell tumor may have spindle and round cells in its stroma, but these are small and



Fig. 60 (P. N. 15404½).—A case of osteolytic sarcoma in a white girl, aged 14, who suffered from pain and swelling of four months' duration in the mid-region of the tibia. *A* shows the characteristic destruction and splintering of the bone with a pathologic fracture. *B* indicates the site of the central vascular cavity which has eroded into the soft parts. An attempt was made to incise the tumor mass in the soft parts of the popliteal space, resulting in a severe hemorrhage. Thirty-six hours later an amputation was performed, and the patient died a few hours afterward.

have not the malignant appearance in their nuclei that is evident in the round and spindle cells just described. 3. Giant cells are sparse in

osteolytic sarcoma and rarely predominate in the section. They are small, usually have less than fifteen nuclei to the cell, and show a tendency to be replaced by giant cells of the malignant tumor type (fig. 67). In benign giant cell tumors the giant cell predominates, and these cells average over fifteen nuclei.

The details of the microscopic appearance of these tumors are best obtained from the photomicrographs shown here. The relative frequency of the occurrence of giant cells in these tumors and the constancy of the findings of the malignant spindle cells or pleomorphic osteoblasts can be judged by consulting the microscopic notes recorded in table 4.

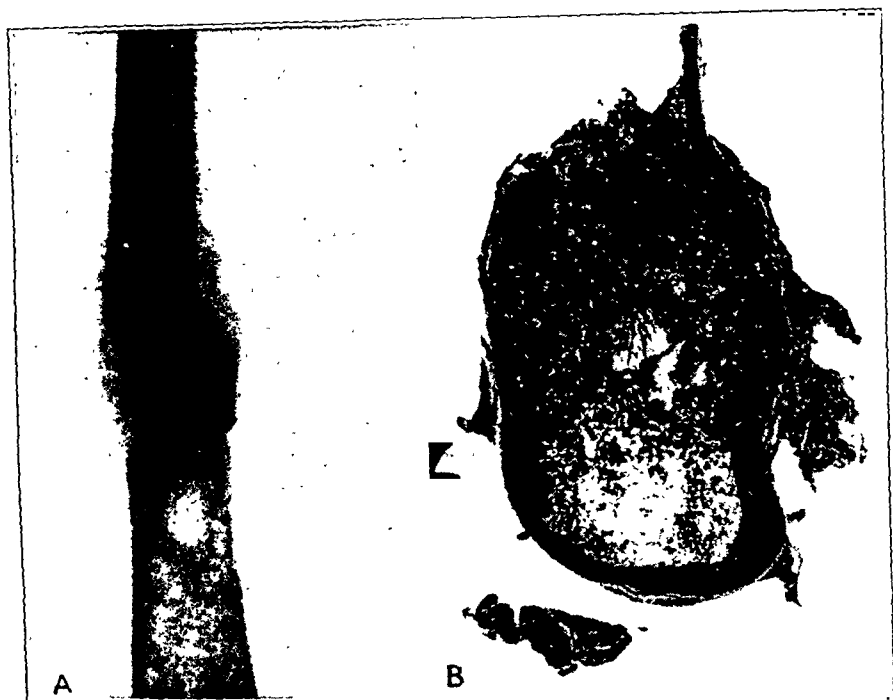


Fig. 61 (P. N. 36456).—A late stage of osteolytic sarcoma simulating metastatic carcinoma. The patient was an adult, aged 39, who died three years after the amputation. *A* shows the destruction of the shaft of the bone by the new growth producing a pathologic fracture. Osseous expansion is not marked, and there are several secondary areas of osseous resorption in the medullary cavity below the lesion. *B* emphasizes the white fibrous nature of the tumor substance invading the shaft above the epiphysis.

It is important to call attention to certain features that set this tumor apart from other forms of sarcoma of the bone. Although in many of the tumors the malignant spindle cell rather than the osteoblasts predominates, this neoplasm can be distinguished from periosteal fibrosarcoma by the fact that the early connective tissue cells do not tend to differentiate into fibroblasts with the whorl formation of fibrillae but



Fig. 62 (P. N. 36456).—Low power photomicrograph showing the central location of the tumor mass depicted in figure 61. The surviving trabeculae of cortical bone are enclosing the neoplastic tissue.



Fig. 63 (P. N. 36456).—High power photomicrograph of the tumor shown in figures 61 and 62. Malignant spindle cells and osteoblasts are invading the fatty bone marrow.

instead are converted into the osteoblasts of the type described. The small amounts of osteoid substance produced is not seen in fibrosarcoma.

Osteolytic sarcoma is distinguished microscopically from the sclerosing form by the sparsity of the osseous substance produced, and by the

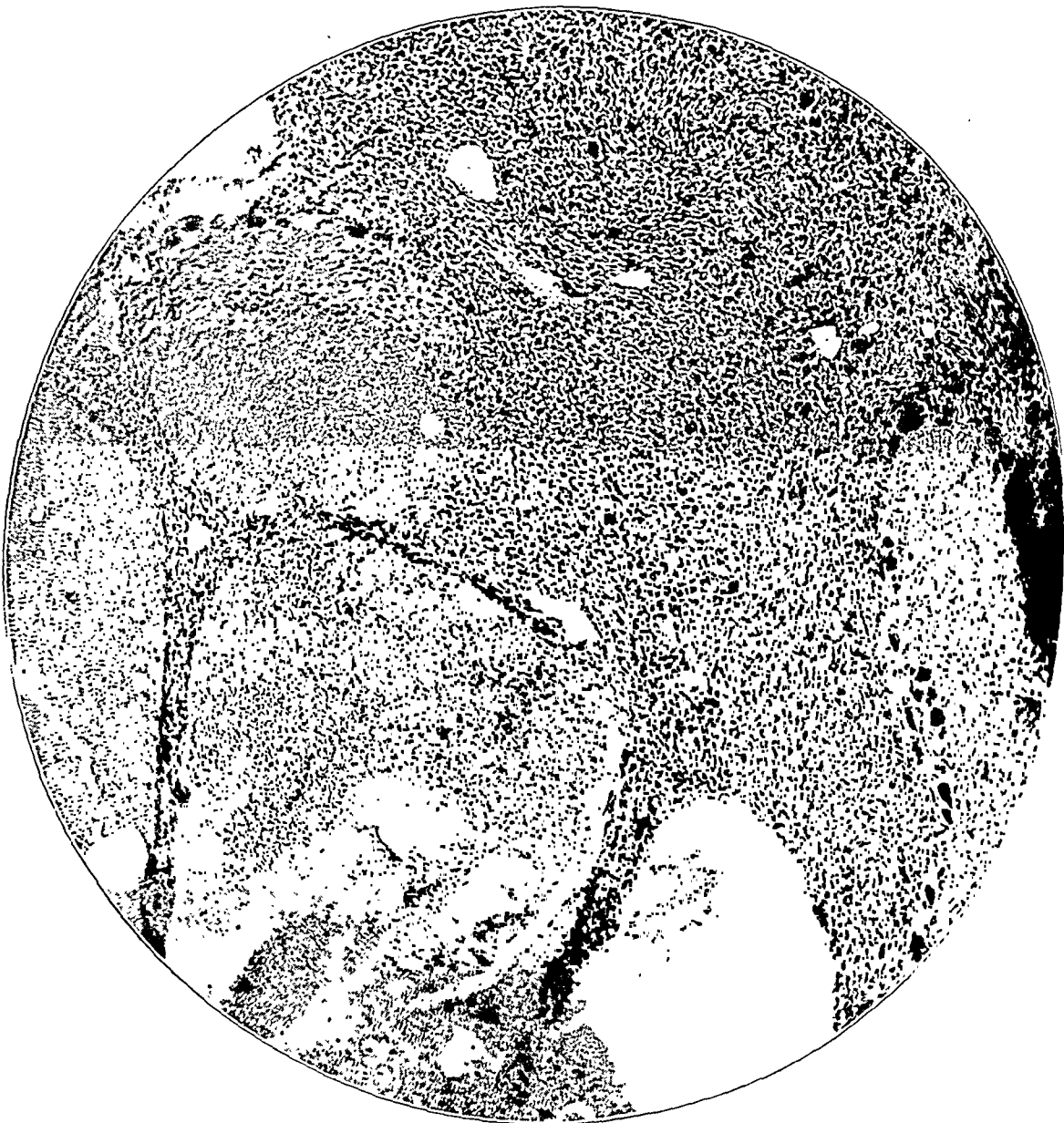


Fig. 64 (P. N. 28574).—Photomicrograph showing the formation of blood spaces rimmed by giant cells found in the vascular areas of osteolytic sarcoma.

fact that the osteoblasts, instead of associating themselves with irregular spicules of newly formed bone, tend to show extreme signs of anaplasia and lie free in a stroma of spindle cells. There is, however, a slight overlap, microscopically, in an occasional case of the so-called

early sclerosing type, which will be discussed under sclerosing osteogenic sarcoma.

Differentiation of this type of sarcoma from the chondral forms is easily made by means of the microscope, as both calcifying cartilage, such as is seen in chondroblastic sarcoma, and myxoma and fetal cartilage, such as is seen in chondrosarcoma, are lacking.

The interpretation of this osteolytic neoplasm as an angiosarcoma is ruled out by the definite signs of ossification of tumorous origin seen in metastatic pulmonary nodules, and the large malignant osteoblasts are not the type of cell seen in hemangiomas that undergo malignant change.

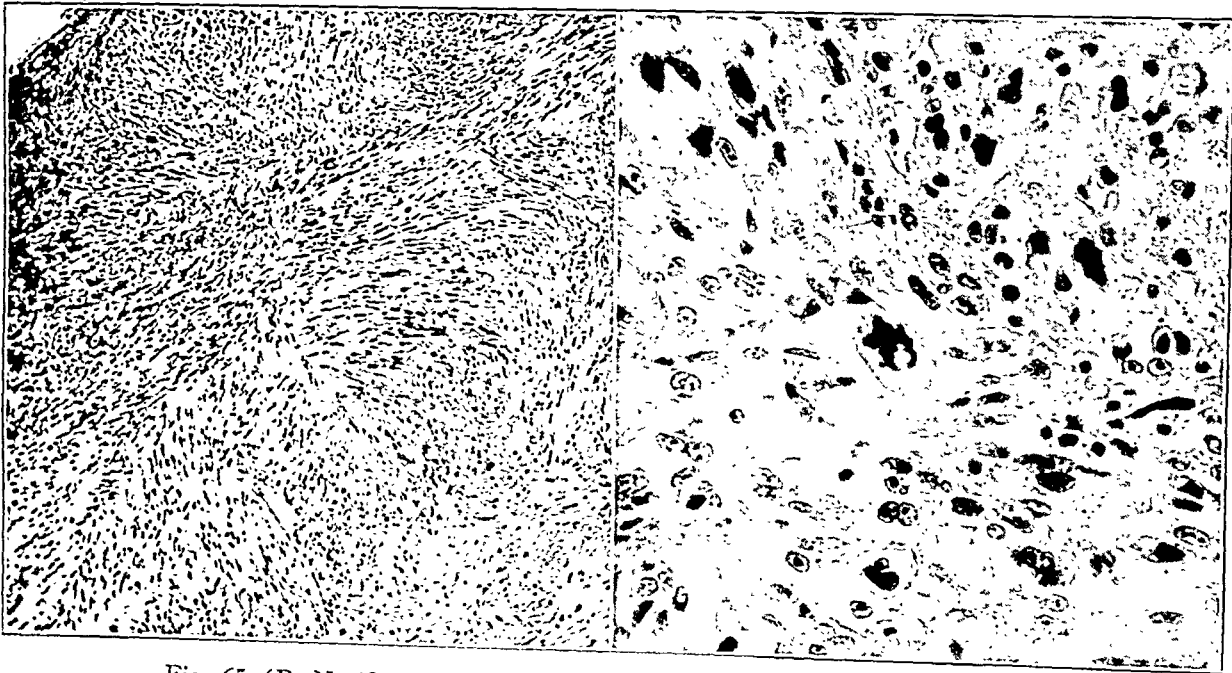


Fig. 65 (P. N. 38882).—Low and high power photomicrograph showing the hyperchromatism and pleomorphism associated with the osteolytic types of osteogenic sarcoma occurring in patients under 30 years of age. The low power photomicrograph emphasizes the connective tissue origin of the neoplasm; the high power, its tendency to differentiate into osteoblasts.

Histogenesis.—A study of the gross specimens and the roentgenograms in the cases of osteolytic sarcoma readily confirms the conclusion that this tumor at its time of origin and in its early phases is confined to the medullary spaces or cancellous structures within the area encircled by the cortical layers of the bone. Microscopic evidence supports the view that the neoplasm represents an early phase of osteogenesis via fibrous tissue. The spindle cells, although showing many signs of pleomorphism and malignancy, differentiate into osteoblasts of an abortive variety, and the tendency toward the production of bone is indi-

cated by the small amounts of osteoid tissue which can be found even in the metastatic pulmonary nodules. In tracing the histogenesis of this tumor, therefore, it is necessary to account for the central origin of the osteogenesis that is in progress and to seek an explanation for the failure of the process to achieve the formation of fully developed new bone and to result instead in a condition characterized by osteolysis.

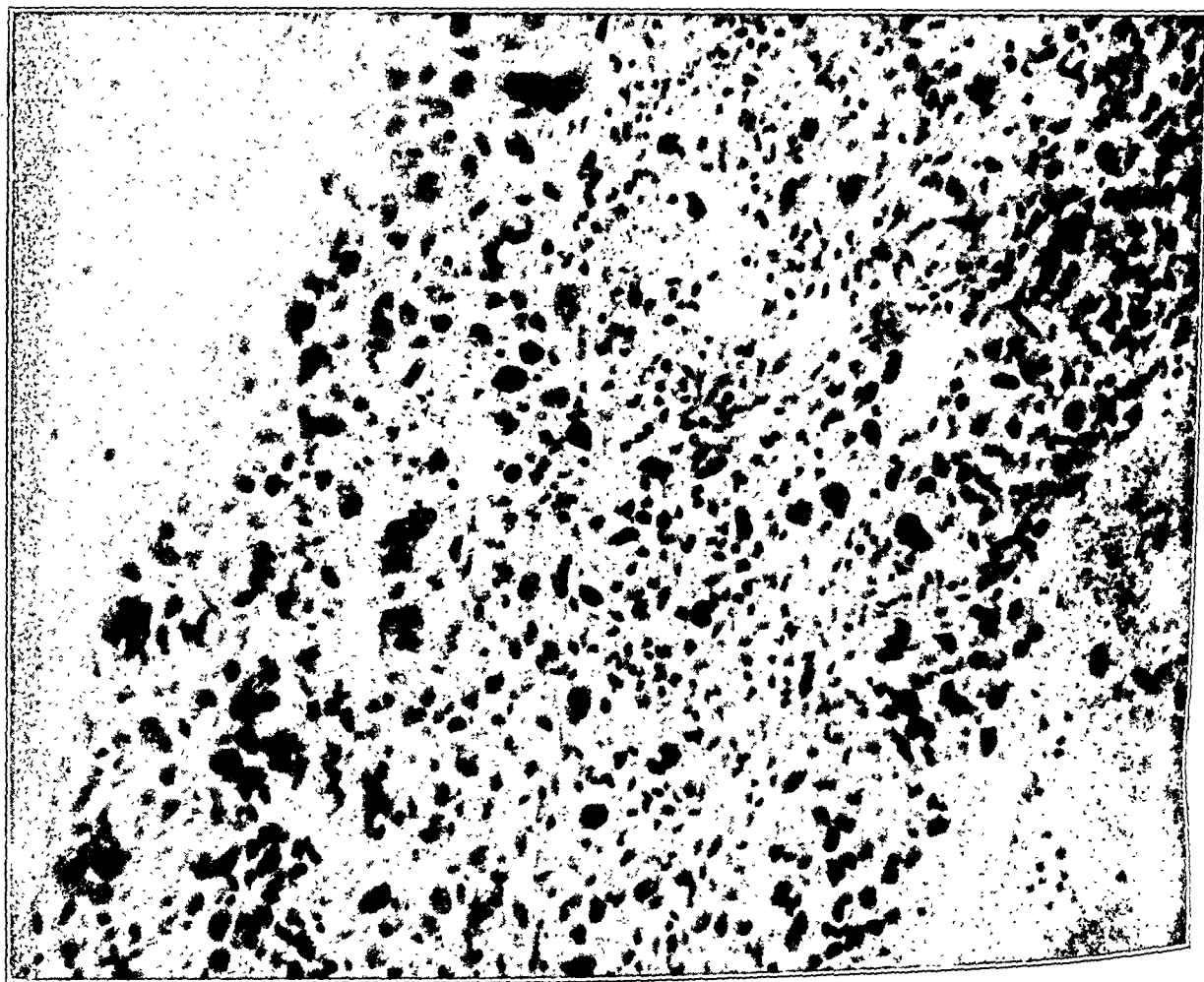


Fig. 66 (P. N. 41194).—Photomicrograph showing the malignant round cells referred to as abortive osteoblasts. Note the vascular spaces associated with the clinical features of aneurysm of the bone.

The answer is to be found in the type and localization of the connective tissue functioning in the regions in which this neoplasm takes its source. This tissue comprises the endosteum of the bone and is concerned in the formation of the cancellous portion of the bone structure that follows on the resorption of calcified cartilage.

In human embryos of from 120 to 140 mm., the sections of the long bones show an early cartilaginous stage of development in the

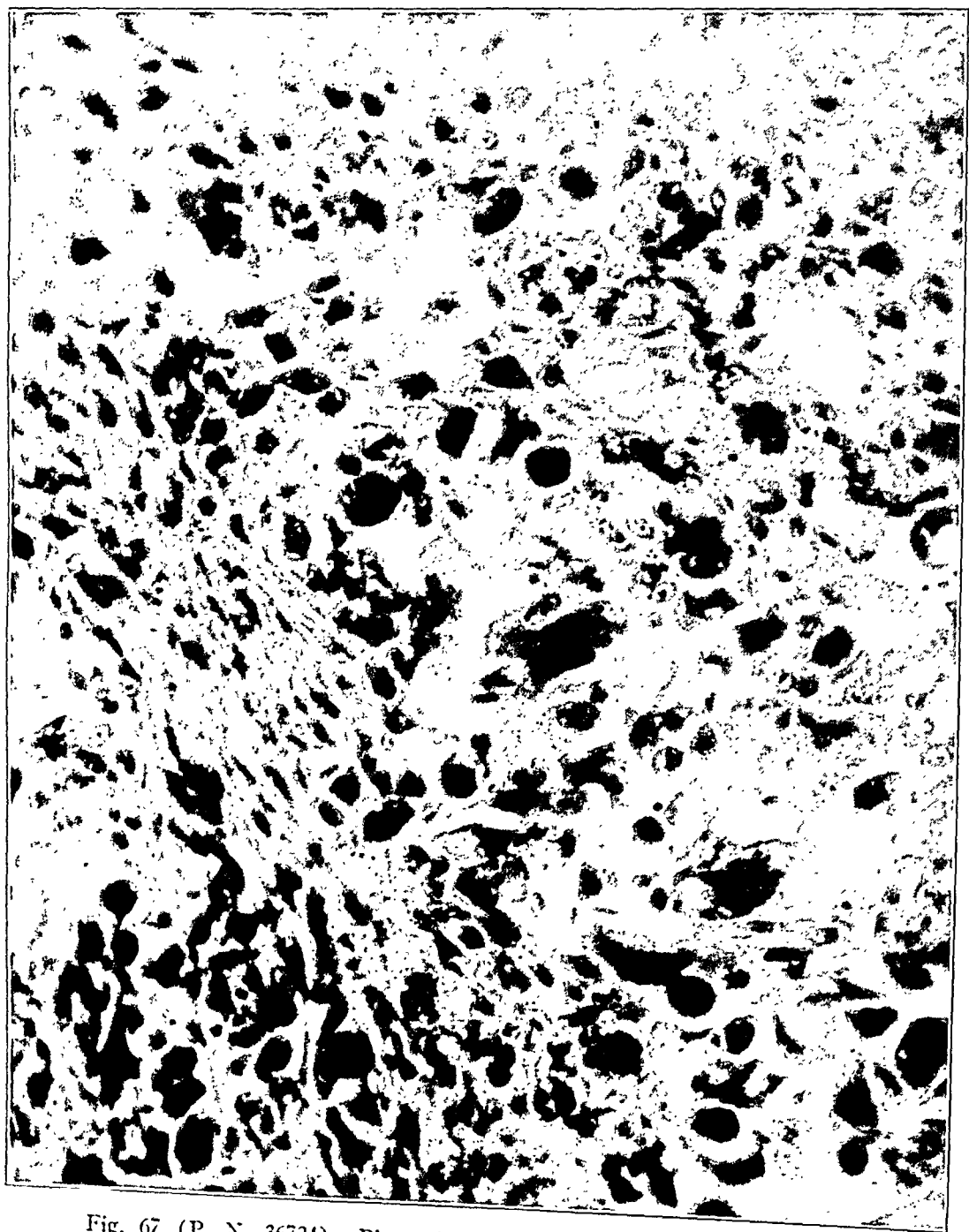


Fig. 67 (P. N. 36724).—Photomicrographs showing the tendency of small giant cells of the epulis type to be associated with malignant tumor giant cells in osteolytic sarcoma. The small giant cells of the epulis type are intermingled with spindle cells and early osteoblasts. The roentgenogram of this case is shown in figure 55.

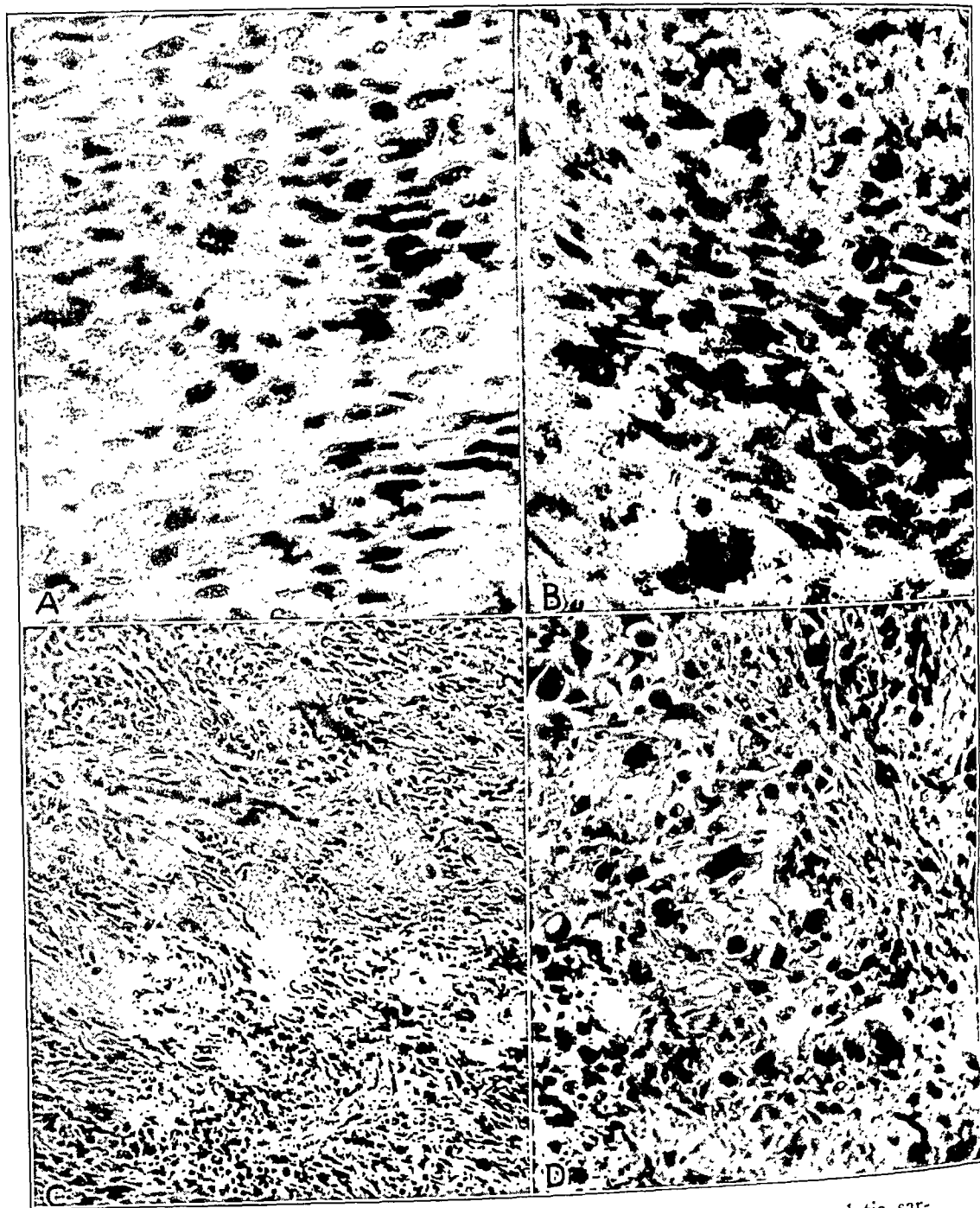


Fig. 68.—Photomicrographs showing the histogenetic cycle in osteolytic sarcoma. *A* shows malignant spindle cells predominating. The nuclei are large and vesicular. Mitotic figures are frequent. *B* shows a structure of malignant spindle and round cells. Abortive osteoblasts predominate. *C* depicts small osteoblasts associated with imperfect bone formation. This section was taken from a metastatic pulmonary nodule and shows more osteoid substance than is usually found in these new growths. *D* pictures a predominance of abortive osteoblasts intermingled with an imperfect osteoid substance which is being resorbed by small giant cells.

skeleton in the regions of the epiphysis and the metaphysis, but throughout the diaphysis of the bone ossification is in progress. At this stage the cortex is being re-formed, perforated by channels of the future haversian system, and the cartilage at the core of the bone is being resorbed to create a vascular cavity. Where a rim of cortical bone can be seen in cross-section, a layer of osteogenic tissue is visible on both sides—the outer layer constituting the periosteum and the inner



Fig. 69.—Cancellous bone formation in a human embryo of 150 mm. The mixture of hemorrhage, giant cells, spindle cells and osteoblasts among the bone spicules shows the same combination of cellular elements found in osteolytic sarcoma arising in cancellous bone.

layer the endosteum (fig. 69). At this stage ossification appears more active on the endosteal side, but the significant fact is that newly formed vessels are prominent, and spindle cells and round cells of the osteoblastic type are abundant, a picture not far removed from that seen in osteolytic sarcoma. The important point is that endosteal ossification following in the wake of calcified cartilage occurs in a tissue composed of a mixture of round and spindle cells and new blood vessels, pre-

senting an appearance similar to osteolytic sarcoma (fig. 70). This process, it is believed, is different from the direct membranous ossification that occurs after the periosteum has become more highly differentiated. It is more rapid, cellular and vascular. It is to be inferred, therefore, that the osteolytic sarcoma arises in ossification of this endosteal type, and its cellular and hemorrhagic character is a constant accompaniment of this primitive postcartilaginous formation of bone.



Fig. 70.—Higher magnification from the same embryo shown in figure 69. This picture emphasizes mixed spindle and round cells in an area of hemorrhage. The bone spicule in the center of the picture is being resorbed.

The failure of the osteolytic type of sarcoma to produce a state of adult bone is to be ascribed to the dependence of ossification in this type of tissue on the presence of calcified cartilage undergoing resorption. While in the embryo the entire core of the future bone provides such a warehouse of cartilage for the storage of calcium, after birth at the age periods when osteolytic sarcoma becomes clinically manifest no such adequate supply of calcified cartilage is available, and the pre-

osseous cellular tissue in the sarcoma readily outstrips the formation of osseous substance. The vessels accompanying this endosteal tissue proliferation may be a factor in eroding the structures of the bone, but in all probability the sarcomatous tissue itself enclosed within the cortical layers may be responsible for pressure atrophy, which in turn opens up numerous vascular channels in the medullary cavity.

The majority of cases of osteolytic sarcoma arise within cancellous bone in the metaphyseal region in patients under 20, which seems to indicate that the neoplasm has its source in a normal growth process concerned in the development of cancellous bone in its metaphyseal region during puberty. The normal growth impetus underlying this sarcoma, when it occurs in young patients, accounts in part for the poor prognosis in persons thus affected.

There is, however, another group of osteolytic sarcomas that are histologically of the same type and that occur in patients over 30, in whom the outlook is not so grave and in whom the duration of symptoms dates back not months but years. The question arises: Is there a secondary form of osteolytic sarcoma which follows on some benign *chronic condition* and which would thus explain this more protracted clinical picture? This question is intimately connected with the problem of so-called metastasizing giant cell tumor, and, as was brought out in a previous contribution,³ in some of these cases of metastatic giant cell lesions the possibility that a secondary sarcoma arose at the site of an unhealed benign lesion must be seriously considered.

Unfortunately, there is no proved case in which microscopic tissue has been preserved when a benign persisting giant cell tumor later gave rise to this form of sarcoma, but the possibility cannot be denied. In some isolated cases the history would seem to indicate that localized areas of Paget's disease or an old fracture might have been the seat of such a secondary malignant growth. All of the patients in this series over 30 years of age have been examined carefully, and the data at hand leaves the matter still in doubt. While in about one third of the cases a residual osteomyelitis, an old fracture or severe trauma many years before or a lesion treated as a benign giant cell tumor is revealed in the history, there is microscopically and in the roentgenogram no evidence by which the benign condition can be definitely connected with the sarcoma that developed later.

The important phases of these supposedly secondary osteolytic sarcomas, regardless of the ultimate status of their etiology, concern the clinical course and ultimate result. As is brought out in the discussion of prognosis and treatment, patients with this secondary form of sarcoma are more apt to be permanently cured by radical operation and even when dying of metastasis may have a postoperative duration of life exceeding five years.

Prognosis and Treatment.—Of eighty-seven cases in the osteolytic sarcoma group, sixty-four were followed more than five years, and those in which the patient may be considered as permanently cured, i. e., living beyond five years, number only four, or about 6 per cent of the total. All of these patients were treated by amputation, usually following an exploratory operation after one or more weeks. In the cases terminating fatally, four of the patients were treated by irradiation either preoperatively or postoperatively without effect, nor did erysipelas and prodigious toxins (Coley's) in the five cases in which it was used affect the ultimate outcome. The striking feature in the cases in which cure was obtained is the age of the patient, which in three of the four cases was 30 years or over, and the duration of the symptoms, which was usually over eighteen months and averaged over four years. This is remarkable, because most of the patients with this form of sarcoma are between the ages of 10 and 20 years and give a history of symptoms of less than one year in duration.

In regard to the curability of this form of osteolytic sarcoma; therefore, one must conclude that only in the exceptional case in which the patient is an adult and the disease has run a protracted course and in which *amputation* preferably without irradiation is employed can favorable results be achieved. Even in such cases there is a possibility that while the patient will live over five years after operation he may ultimately succumb to metastasis. There are four such patients in this series, who lived from five to seven years after operation, but who finally died with pulmonary metastases. These four cases have not been included in the five year cures although possibly they are entitled to consideration as such, and if so considered would raise the percentage of cures in this group to 12 per cent. In each instance of these protracted cases the initial diagnosis was a benign giant cell tumor; and the original sections showed many giant cells. This mistaken diagnosis also was made in one of the cases placed among the bona fide five year cures.

In the younger patients, regardless of the form of therapy, the duration of life after treatment may usually be prophesied according to the duration of symptoms before examination. In this series the symptoms average eleven months and the postoperative duration of life an equal period, giving a total clinical course of something under two years.

The prognosis and results of treatment in the more chronic forms of osteolytic, osteogenic sarcoma occurring in adults are similar to the results of treatment analyzed in secondary chondrosarcoma, and support the inference that the more slowly growing and more readily curable instances of this disease are secondary to some preceding benign lesion.

THE SCLEROSING FORM OF OSTEOGENIC SARCOMA

The most highly differentiated periosteal sarcoma is the osteoblastic or sclerosing type. This osteoblastic or sclerosing form is the most emphatic bone-forming tumor in the group of osteogenic sarcoma, since it arises in the subperiosteal tissues capable of direct osseous formation. It is this particular tumor, characterized in the x-ray film by dense, shaggy new bone in the periosteal zone near the ends of the long bones in patients between the ages of 10 and 25 years, with which clinicians and roentgenologists are most familiar, and which is most commonly diagnosed correctly as sarcoma of the bone. Microscopically, large round cells or osteoblasts producing an abundant matrix of osteoid tissue are responsible for the new growth.

Clinical Features.—Although the sclerosing form of osteogenic sarcoma with its "sun-ray" appearance in the roentgenogram is the most universally recognized type, it is not the most frequent and ranks third, with 75 cases among a total of 360 osteogenic sarcomas forming the basis of this study. Among the clinical features of this group, the narrow age limits, the characteristic location and the brief duration of the symptomatology are outstanding. The majority of patients with sclerosing sarcoma of the bone are between the ages of 15 and 25 years. In the series under analysis, 41 cases occurred in this decade, 16 in the preceding decade (from 5 to 15 years) and 9 in the succeeding decade (from 25 to 35 years). There were only 5 cases in persons not in these three decades: a congenital tumor was discovered in the femur of a baby 16 days old (fig. 71) and the others were elderly adults (table 5). Most of the lesions were situated in either the lower end of the femur or the upper end of the tibia, nearly 80 per cent of the tumors being thus accounted for. The remainder occurred in the upper extremity, with a few isolated cases in the ribs and vertebrae, the pelvis and about the skeletal trunk. The most striking feature of the location of these tumors, however, is not the bone affected, but the region of the bone involved. The favorite site of origin of these growths is neither the shaft nor the epiphysis, but the metaphyseal side of the epiphyseal line. The significance of this distribution is strikingly emphasized by the study of the histogenesis of these tumors which is presented subsequently.

The duration of symptoms in this group of sarcomas of the bone averages under ten months. Trauma, pain, tumor and dysfunction are the usual sequence of events, trauma occurring at the onset of approximately one half the cases adequately recorded. Pathologic fracture is rare and was listed only five times in the present series. Examination of the affected extremity usually shows a visible and palpable swelling of bony hardness near the end of the bone. Cutaneous changes are not marked over tumors of moderate size, and the slight limitation of motion

TABLE 5.—*Osteogenic, Sclerosing Sarcoma*

P. N.	Race, Sex and Age	Location	Duration, Mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Result
42852	W F 35	Femur, lower	16	Pain, tumor, limp	Sclerosing periosteal	Amputation, May, 1930	Ossification, osteoblasts, spindle cells, cartilage
42180	W F 17	Femur, lower	6	Pain, tumor, limp	Sclerosing periosteal	Amputation, Nov. 2, 1929	Ossification, osteoblasts
40876	W M 18	Tibia, upper	2½	Tumor, pain	Sclerosing periosteal	Amputation, advised Sept. 12, 1928	Ossification, osteoblasts
40706	W F 19	Tibia, upper	Sclerosing periosteal	Amputation, Aug. 15, 1929	Ossification, osteoblasts, spindle cells, cartilage
40318	W F 19	Femur, lower	Sclerosing periosteal	Excision, Aug. 15, 1929	Ossification, osteoblasts, spindle cells, cartilage
40026	W F 9	Ilium, right	5	Pain, tumor	Sclerosing periosteal	Preoperative irradiation; colloidal lead, Jan. 18, 1928	Ossification, osteoblasts, spindle cells	Dead 9 mos. after amputation
39794	W M 15	Femur, lower	1½	Tumor	Increased density, parallel periosteal reaction, expansion	Amputation, December, 1927	Ossification, osteoblasts, spindle cells	Dead after operation
39462	W F 14	Tibia, upper	1½	Pain, tumor	Sclerosing periosteal	Cauterization, June 30, 1927; amputation, July 16, 1927	Ossification, osteoblasts, spindle cells	Well almost 3 yrs. later
39382	W F 16	Humerus, upper	6	Trauma, pain, tumor	Sclerosing periosteal	Amputation, April, 1927	Ossification, osteoblasts, spindle cells	Dead 18 mos. later
39114	W M 21	Femur, lower	3½	Tumor, pain	Sclerosing periosteal	Amputation	Ossification, osteoblasts, spindle cells	Dead 6 mos. later
38566	W M ..	Femur, shaft	2	Sclerosing periosteal	Exploration, amputation, Sept. 13, 1926	Ossification, osteoblasts, spindle cells	Dead 4½ mos. later
38352	W M 26	Femur, lower	36	Trauma, pain, tumor	Sclerosing periosteal	Excision, May 31, 1926 (complete, including end of radius)	Ossification, osteoblasts, spindle cells	Dead 1 yr. later
37938	W M 7	Radius, lower	1	Tumor	Sclerosing periosteal	Amputation, October, 1926	Ossification, osteoblasts, spindle cells
37882	C M 16	Tibia, upper	..	Trauma	Sclerosing periosteal	Preoperative irradiation and resection advised, Dec. 30, 1925	Ossification, osteoblasts	Dead 5 mos. later
37450	W M 24	10th rib, right	6	Trauma, tumor, pathologic fracture	Sclerosing periosteal	Exploration and amputation, Nov. 30, 1925	Ossification, osteoblasts	Dead 6 mos. later
37178	W F 18	Femur, shaft, right	10	Trauma, pain, tumor	Sclerosing periosteal	Exploration and amputation, Nov. 10, 1925	Ossification, osteoblasts	Well 5 yrs.
37018	W M 15	Tibia, upper	4	Trauma, pain, tumor	Sclerosing periosteal	Exploration and amputation, July 10, 1925	Ossification, osteoblasts	Dead 3 mos. later
36848	W F 10	Humerus, lower shaft, right	2	Pain, tumor	Sclerosing periosteal	X-ray, May 18, 1925	Ossification, osteoblasts, spindle cells	Dead 21 mos. later
36556	W 16 days	Femur, upper left	Con: Pathologic fracture, genital tumor	Sclerosing periosteal	Amputation, Nov. 6, 1924	Ossification, osteoblasts, spindle cells	Dead 3 mos. later
36112	W F 13	Humerus, upper	4	Trauma, tumor, pain	Sclerosing periosteal	Amputation, Nov. 3, 1924	Ossification, osteoblasts, spindle cells	Dead 13 mos. later
35786	W M 15	Femur, right	3	Pain, tumor	Sclerosing periosteal	Irradiation, July 30, 1924	Ossification, osteoblasts, spindle cells	Local recurrence: dead 7 mos. later
35694	W M 26	Femur, shaft, right	Sclerosing periosteal	Amputation, Sept. 22, 1924	Ossification, osteoblasts, spindle cells	Dead 17 mos. later
35672	W M 25	Femur, lower	1½	Trauma, pain	Sclerosing periosteal	Cauterization, Sept. 8, 1923; amputation, Sept. 21, 1923	Ossification, osteoblasts, spindle cells
35140	W M 15	Femur, lower shaft	Sclerosing periosteal

No.	Sex	Age	Site	History	Operation	Pathology	Prognosis
3434	W	M	15	Femur, lower shaft	Amputation	Sclerosing periosteal	Dead after operation
3430	W	M	15	Femur, lower	Curettement, Sept. 8, 1923; amputation, Sept. 21, 1923	Sclerosing periosteal	Dead 17 mos. later
3429	W	M	54	Vertebra, 2d and 3d	Irradiation, 1920	Sclerosing periosteal	Dead 18 mos. after appearance of symptoms
3410	W	M	22	Femur, lower	Amputation, Oct. 25, 1923	Sclerosing periosteal	Dead 2 mos. later
3425	W	M	10	Scapula, right	Amputation, Oct. 25, 1923	Sclerosing periosteal	Dead 18 mos. after onset
3307	W	M	19	Fibula, upper	Excision, radium, amputation	Sclerosing periosteal	Dead 5 mos. after excision
3279	W	F	14	Femur, lower	Irradiation, April 17, 1923	Sclerosing periosteal	Dead 15 mos. later
3212	W	M	18	Femur, lower	Amputation, Jan. 5, 1923	Sclerosing periosteal	Well 4 yrs., 10 mos. later
3195	W	M	15	Fibula, upper left	Amputation, Dec. 11, 1922; amputation, Dec. 18, 1922	Sclerosing periosteal	Well 5 yrs., 9 mos. later
3182	W	F	..	Femur, lower	Excision, Dec. 11, 1922; amputation, Dec. 18, 1922	Sclerosing periosteal	Dead 11 mos. after amputation
3189	W	F	8	Humerus, upper left	Amputation, Jan. 5, 1923	Sclerosing periosteal	Dead
3050	C	M	6	Femur, lower	Exploration, excision	Sclerosing periosteal	Dead after second operation
3016	W	M	20	Femur, upper right	Exploration, June 17, 1922; amputation, Dec. 29, 1922	Sclerosing periosteal	Dead 1 yr. after amputation
3054	W	F	38	Rib, fourth	Irradiation, amputation, Dec. 1, 1921	Sclerosing periosteal	Well 8 yrs. later
3018	W	M	13	Femur, lower	Amputation, Nov. 4, 1921	Sclerosing periosteal	Dead in less than 1 yr. after appearance of symptoms
2963	W	M	25	Femur, shaft	Amputation, Nov. 4, 1921	Sclerosing periosteal	Lost
2900	W	F	25	Femur, lower	Exploration, July 19, 1921; amputation, July 20, 1921	Sclerosing periosteal	Well 6½ yrs. later
2891	W	F	19	Tibia, upper	Amputation, Dec. 10, 1919	Sclerosing periosteal	Dead 2 yrs., 4 mos. later
2852	W	M	67	Ulna, olecranon	Amputation, May, 1918	Sclerosing periosteal	Dead nearly 7 yrs. later
2821	W	F	34	Femur, lower	Amputation, Jan. 2, 1913	Sclerosing periosteal	Well almost 12 yrs., lost
2828	W	F	27	Radius, upper left	Amputation, April 5, 1921	Sclerosing periosteal	Dead 2 yrs., 9 mos. later
2753	W	F	30	Femur, lower	Aspiration, Jan. 25, 1921; radium and irradiation; amputation, May 20, 1921	Sclerosing periosteal	Well over 9 yrs.
2757	W	F	6	Femur, lower left	Preoperative x-ray; partial excision, Dec. 30, 1920; postoperative irradiation, radium	Sclerosing periosteal	Dead 6½ mos. after operation
2735	W	F	16	Skull, parietal left		Sclerosing periosteal	

TABLE 5.—*Osteogenic, Sclerosing Sarcoma—Continued*

TABLE 5.—Osteogenic, Sclerosing Sarcoma									
Race, Sex and Age	Location	Duration, Mos.	Symptoms	Roentgen Findings	Treatment		Microscopic Findings	Result	
W M 15	Clavicle, midpart	3	Trauma, pain, tumor	Sclerosing periosteal, slight osseous destruction	Excision, Sept., 1920; preoperative x-ray		Ossification, osteoblasts, spindle cells	Well nearly 10 yrs. later	
W M 15	Clavicle, midpart	3	Pain, swelling	Sclerosing periosteal	Excision, Sept., 1920; preoperative x-ray		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 18	Tibia, upper	36	Trauma, pain, tumor	Sclerosing periosteal	Amputation, Aug. 2, 1919		Ossification, osteoblasts, spindle cells	Dead 1½ mos. later	
W F 16	Rib, 11th right	3	Trauma, pain, tumor	Sclerosing periosteal	Amputation, Aug. 2, 1919		Ossification, osteoblasts, spindle cells	Dead 3¼ mos. later	
W M 18	Femur, upper	..	Pain, tumor	Sclerosing periosteal	Amputation, July, 1919; higher amputation, March 4, 1920		Ossification, osteoblasts, spindle cells	Dead 4 yrs., 8 mos. later (other causes)	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, July, 1919; higher amputation, March 4, 1920		Ossification, osteoblasts, spindle cells	Dead 2½ yrs. after second amputation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Well 6 yrs., lost	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 12 yrs. after amputation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 10 mos. later	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 3 mos. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
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W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
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W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower	3	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W F 20	Femur, lower	2	Tumor	Sclerosing periosteal	Amputation, March 9, 1920		Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation	
W M 18	Femur, lower								

in the adjacent joint is of no clinical significance. Occasionally crepitus may be elicited by pressure on the bony spicules of the growth, but such manipulations are not to be encouraged when x-ray studies are available.

In one fifth of the cases leukocytosis or fever or both were recorded, which is about the usual incidence of these systemic reactions in rapidly



Fig. 71 (P. N. 36566).—Roentgenogram of a sclerosing osteogenic sarcoma occurring at birth in the metaphysis of the upper end of the femur. The baby was 16 days old when the film was made. There is marked periosteal new bone and secondary osseous destruction.

growing malignant neoplasms of the bone whether the patients are seen in either the earlier or later stages of the disease. No particular diagnostic importance should be attached to such findings unless the temperature equals or exceeds 102 F. and the leukocytes 20,000; above these limits, infection is to be suspected.

Roentgenographic Features.—The x-ray film furnishes the most helpful diagnostic data available to the practitioner in this group of cases. The usual roentgenogram of a bone affected with this form of osteogenic sarcoma shows an area on the shaft side of the epiphyseal line of a long bone (generally the lower end of the femur or the upper end of the tibia) in which dense formation of new bone is obliterating the normal osseous markings. In the marrow cavity, this sclerosis is

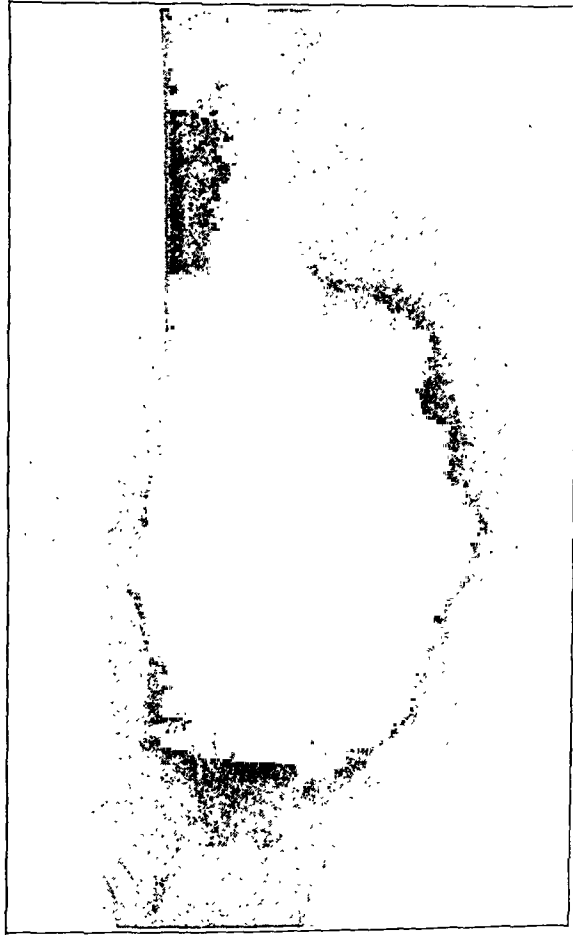


Fig. 72 (P. N. 29000).—A roentgenogram of sclerosing sarcoma showing marked sclerosis in the marrow cavity and periosteal zones. The patient had had symptoms of over eleven months' duration and lived over five years after amputation.

accompanied by some secondary destruction of the bone which may produce a slight mottling effect. In the cortical zone, the normal transition between marrow and cortex is usually obscured in the affected area by the osseous formation which extends into both medullary and periosteal zones. The periosteum above and below the main area of the tumor is raised, and where it resumes its contact with the bone, a triangle of



Fig. 73 (P. N. 36848).—An early case of sclerosing sarcoma occurring in a child of 10. The roentgenograms show new bone localized in the subperiosteal region of the metaphysis. In the gross specimen the cortex of the marrow cavity has not been invaded by the tumor. The lesion had been present two months before treatment, and the patient is living over five years after a resection of the lower end of the humerus.

ossification appears, known as periosteal lipping. Although this so-called lipping has been much stressed as a diagnostic feature of sarcoma, it is not rare in forms of periostitis unrelated to neoplastic disease.

The most striking affects are in the region of maximal periosteal separation, where radiating spicules of new bone, proceeding outward



Fig. 74 (P. N. 39114).—An early case of sclerosing sarcoma in which subperiosteal formation of new bone in the metaphyseal region predominates. The roentgenogram differs from chondrosarcoma in that slight sclerosis of the marrow cavity is present. The gross specimen shows clearly the fresh white osteoid substance and the slightly increased density in the cancellous bone beneath the cortex. This patient had symptoms of three and one-half months' duration, and is living approximately one year after amputation.

at right angles, are crowded together to give the characteristic shaggy, sun-ray appearance (fig. 72).

In studying a large series of x-ray films of cases in which the diagnosis was verified by pathologic examination, the roentgenograms may be grouped according to the duration of symptoms and the early and late phases of the growth compared. In the early cases of from two to four month's duration (figs. 73 and 74), the tumor is largely confined to a subperiosteal location, in which delicate radiating lines of new bone are visible beneath an area of raised periosteum, the cortex and marrow cavity being practically undisturbed. In the advanced cases



Fig. 75 (P. N. 30616).—A late case of sclerosing sarcoma occurring in a patient, aged 20, who had symptoms of two years' duration and who died twelve months later after an amputation at the hip joint. The roentgenogram shows marked sclerosis of the marrow cavity and the gross specimen, secondary destruction of the bone with pathologic fracture.

of from six to twelve months' duration (figs. 72 and 75), on the other hand, the periosteal new bone is not only more dense but the cortex and marrow cavity beneath are invaded and sclerosed and the growth extends lengthwise along the shaft. Areas of secondary destruction of the bone and pathologic fracture may eventually occur. It is clear from an analysis of the roentgenograms that the site of the origin of the tumor

is in the metaphyseal region in the subperiosteal zone of the long bones, where osteogenesis is proceeding most rapidly at the age period when these tumors occur.

Gross Specimens.—The gross specimens secured at operation by amputation provide one of the most valuable means of studying the origin and growth of this type of sarcoma of the bone. In all of the specimens available for study, twenty-two in all, the tumor proper was situated in the metaphysis, and the epiphysis was never primarily involved. In young patients with an unossified epiphyseal line, the epiphyseal cartilage walls off the tumor in that direction, and even in the advanced stages the epiphysis remains free while the growth extends



Fig. 76 (P. N. 30616).—Low and high power photomicrographs showing the large osteoblasts applied to the osteoid intercellular substance, typical of sclerosing sarcoma. (Same case as shown in figure 75.)

instead outwardly into the soft parts and upward along the shaft of the bone (fig. 77). In older patients, when the epiphysis has united, secondary involvement of the end of the bone occurs when the tumor has progressed without early operative intervention.

In early cases the bulk of the sarcomatous growth is found between the periosteum and the cortex of the bone on the shaft side of the epiphyseal line. The tumor tissue is firm in consistency, varying in density from that of solid fibrous tissue to the hardness of compact bone. Its structure shows a definite grain or fiber which runs outward from the shaft, more or less at right angles to its long axis (fig. 78).

The color is white, light gray or whitish pink. Hemorrhage, either old or recent, and cyst formation are practically always absent, unless the tumor has previously been explored. The ossifying neoplastic tissue is decidedly gritty to the touch and cuts poorly, or not at all when the knife is applied. At its extreme margin the raised periosteum bounding the tumor may be perforated, and the muscle invaded by white solid tumor tissue. This outer zone shows the most fibrillated structure with individual spicules of bone arranged in a radiating manner. As the cortex is approached, the tumor is more solid and assumes the structure of compact bone, its cut surface in these areas often appearing as frozen or like caked snow (fig. 74).

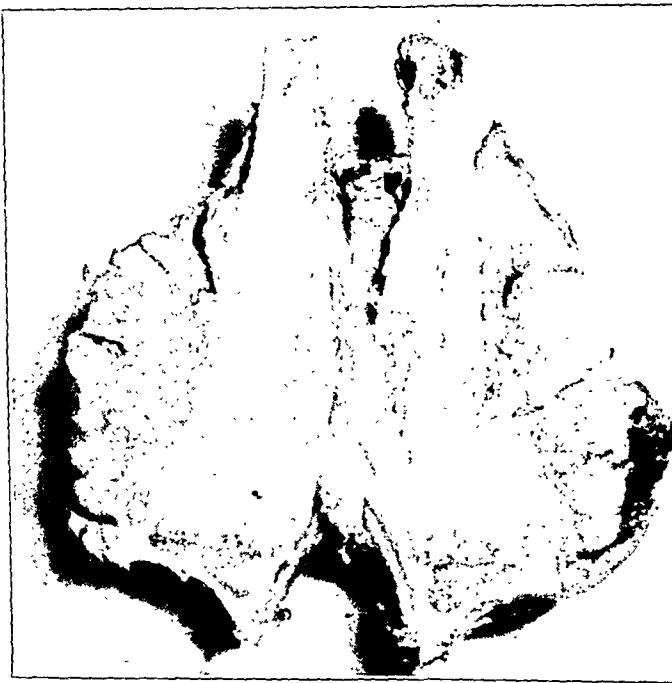


Fig. 77 (P. N. 37938).—A gross specimen of sclerosing sarcoma in a boy, aged 7. The pronounced formation of new bone which infiltrates into the marrow cavity and soft parts is effectively walled off by the cartilage of the unossified epiphyseal line.

Invasion of the medullary cavity is apparently secondary to the subperiosteal growth. The earliest change seen in the medullary cavity is the production of normal bone which reacts vigorously to early invasion of the tumor. This sclerosis of the medullary cavity, which is due to a combination of both the tumor bone and reactive bone, is generally less in amount than the subperiosteal tumor growth, but in rare instances may keep pace with it. As the tumor progresses, the neoplastic tissue gives rise to more and more compact bone, which although at first largely confined to the zone beneath the periosteum in a metaphyseal

location later extends throughout the entire area of the tumor, in the medullary cavity, in the subperiosteal regions and even in the soft parts. It is this picture of diffuse osseous consolidation seen in advanced cases that caused the older pathologists to apply the name of sclerosing sarcoma to this new growth.

Microscopic Features.—The microscopic studies confirm the view that the neoplastic process in this sarcoma involves tissue concerned in



Fig. 78 (P. N. 24856).—Gross specimen of a cured case of sclerosing sarcoma in a white girl, aged 20. This specimen shows the radiating fibers of the tumor mass proceeding outward from the cortex beneath the periosteum in the metadiaphyseal region of the bone.

direct osseous formation. The histology of all these lesions is essentially proliferation of connective tissue passing through the stages of spindle cells, osteoblasts, osteoid tissue and new bone. Most of the sections are predominated by a proliferation of many osteoblasts with large deep staining vesicular nuclei and a cytoplasm pointed in one direction like the tail of a tadpole (fig. 79). Among these cells, a deep staining osteoid substance is found. This direct mode of ossification differs in

these sarcomas from benign reactive bone seen in inflammatory conditions and osteitis fibrosa in two outstanding respects. First, the osteoblasts predominate and great numbers are packed in among the

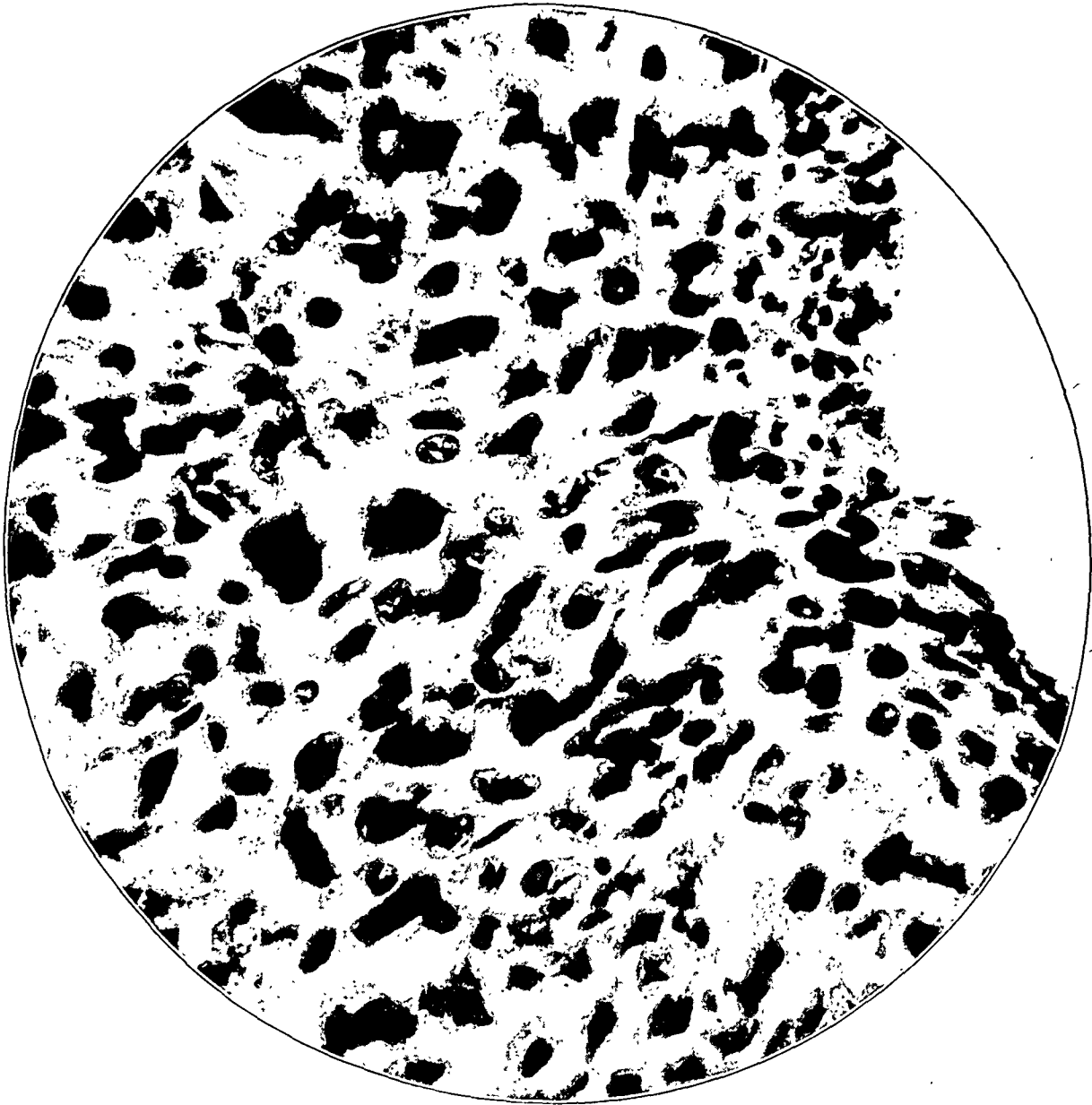


Fig. 79 (P. N. 14817).—Proliferation of numerous malignant osteoblasts in a case of sclerosing sarcoma. The osteoblasts have no definite relation to either bone spicules or osteoid substance.

osteoid tissue in a disorderly fashion. Unlike benign osseous formation of the membranous type, the osteoblasts vary in size, giving rise to numerous large binucleated forms, and they are not lined in orderly

rows about definitely formed bone spicules (compare figs. 79 and 80). Second, the osteoid tissue is laid down helter-skelter and bears no constant relationship to the amount of fibrous tissue or osteoblasts present. In some sections this osteoid substance may infiltrate everywhere, compressing the masses of osteoblasts between it. In other sections the

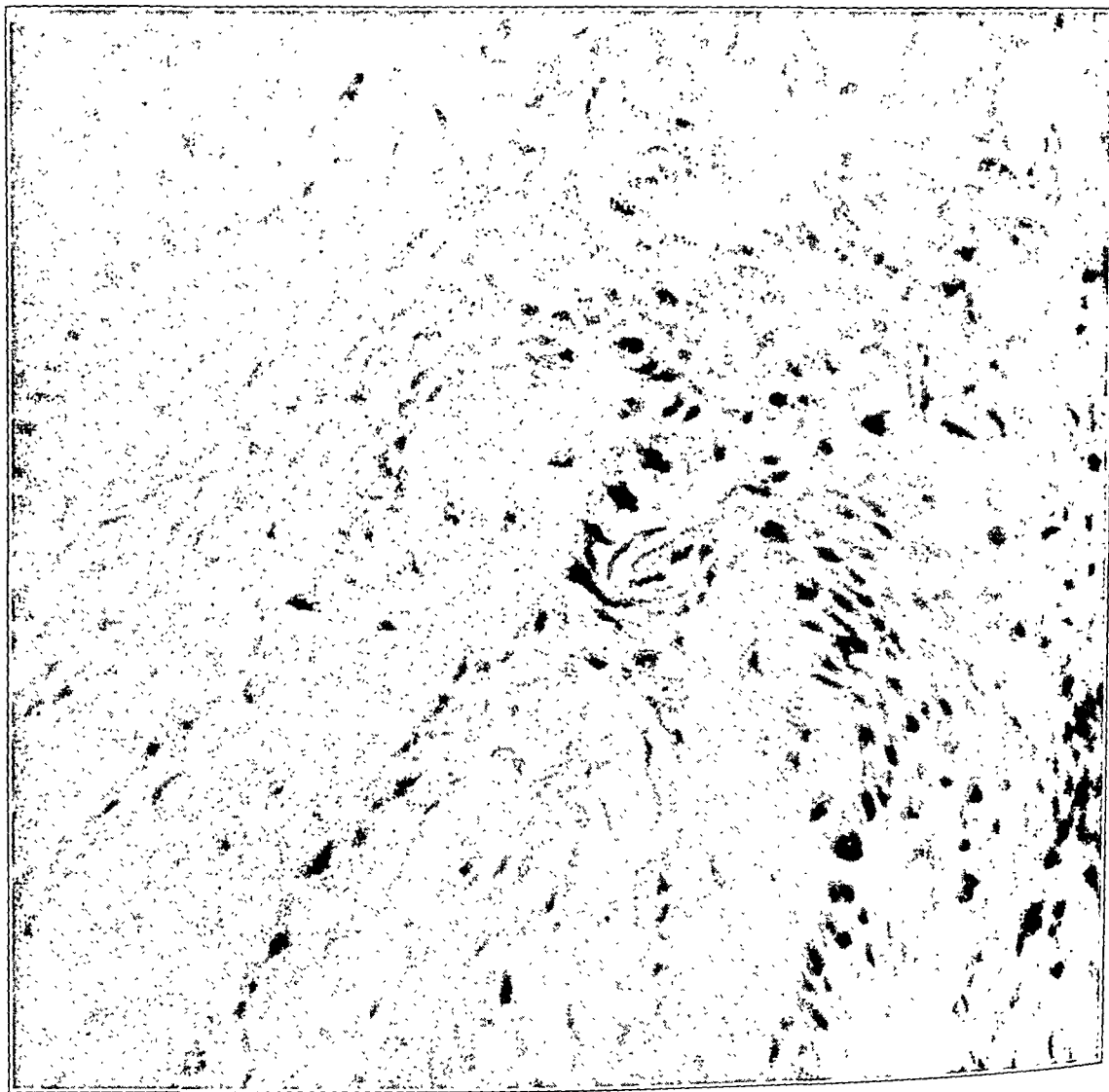


Fig. 80 (P. N. 14179).—The osteoblasts in new bone of the normal reactive type. The osteoblasts are relatively small, are associated with a preceding connective tissue containing many spindle cells and fibroblasts and are arranged in orderly rows about definite spicules of new bone. (Figures 79 and 80 demonstrate a comparison of the type of osteoblasts seen in malignant and normal bone formation.)

osteoid tissue may be relatively sparse, and the osteoblasts and their precursors the fibroblasts may predominate, the osteoid substance being present only in scattered areas (fig. 81).

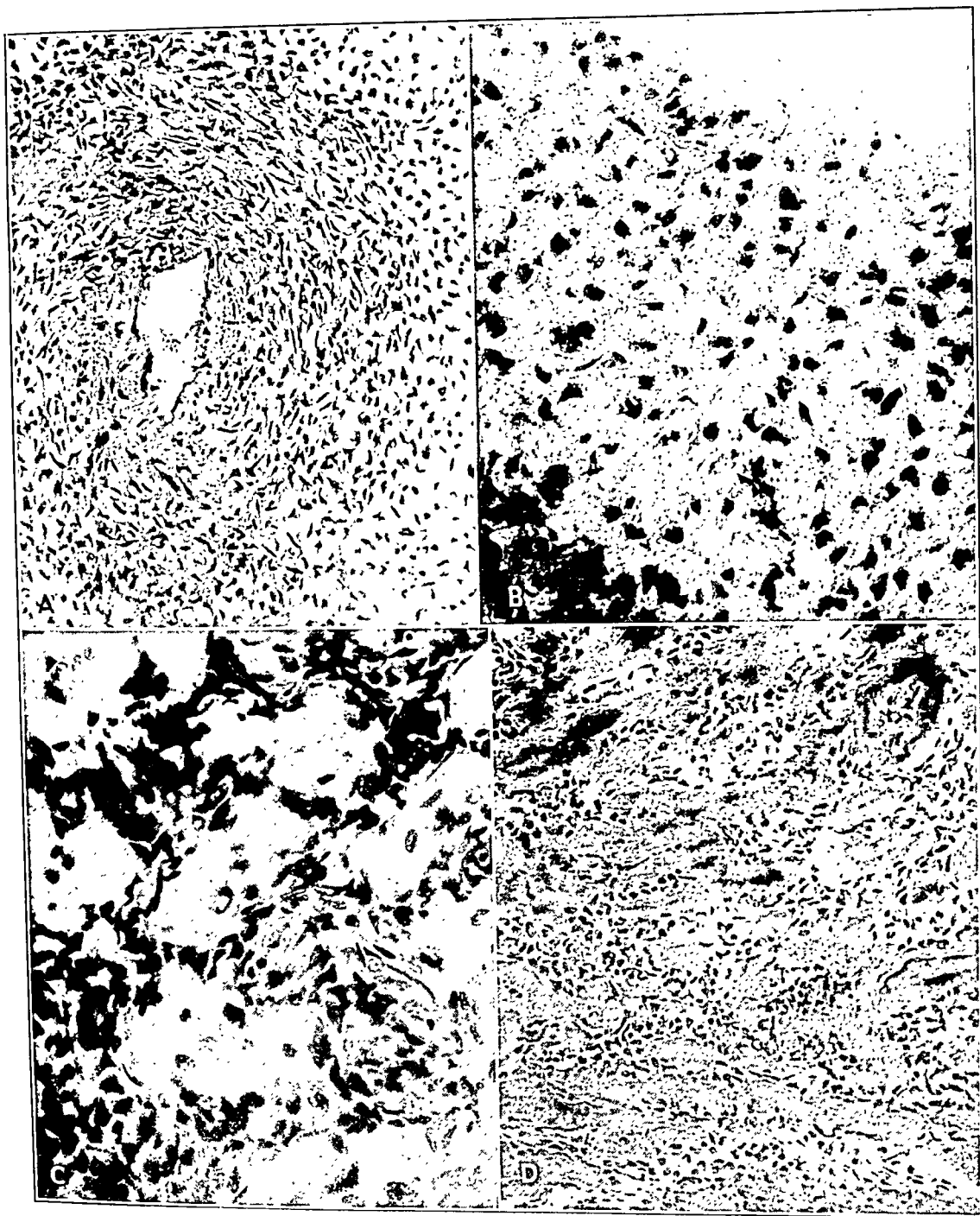


Fig. 81.—The histogenetic cycle of sclerosing osteogenic sarcoma. *A* shows the pre-osseous edema among malignant spindle cells and early osteoblasts, surrounding a small blood vessel. *B* shows definite osteoid material surrounding the cells which are predominantly osteoblasts. *C* shows the osteoid substance in early and indefinite spicule arrangement surrounded by malignant osteoblasts and spindle cells. *D* shows the formation of definite but irregular osteoid spicules, surrounded by a profusion of malignant osteoblasts.



Fig. 82 (P. N. 14817).—Photomicrograph of an area in the same case shown in figure 79. The osteoblasts and spindle cells are grouped about blood vessels to give a characteristic perithelial arrangement.

While in the usual sclerosing osteogenic sarcoma, the microscopic features emphasize a highly differentiated type of osteogenesis characterized by direct formation of bone with a predominance of osteoid and osseous substance among a proliferation of osteoblasts; some of these tumors, despite their periosteal location, may show a slightly earlier

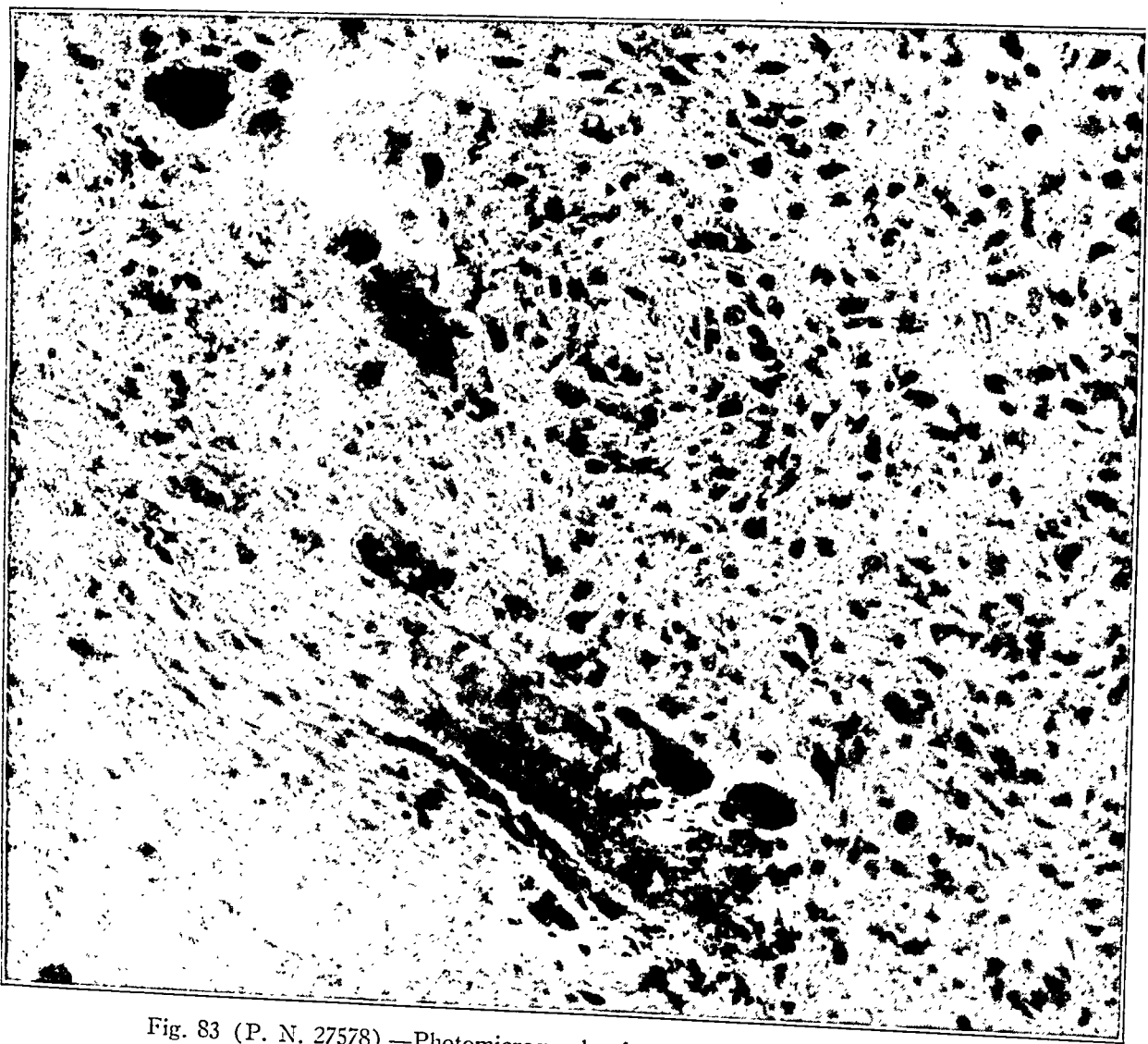


Fig. 83 (P. N. 27578).—Photomicrograph of a section taken from the margin of a sclerosing osteogenic sarcoma showing spicules of normal reactive bone being laid down beside an area of malignant osteoblasts intermingled with early osteoid substance. At the middle of the picture normal bone formation proceeding from the left is meeting malignant bone formation from the right. The result is the destruction of the normal bone spicules and their resorption by giant cell osteoclasts.

histogenetic phase. This early phase of the sclerosing form of osteogenic sarcoma is microscopically identical with the osteolytic form previously described. These tumors are rare and will be discussed subsequently

when variants of sclerosing sarcoma are considered. In fully developed cases, however, vascular tissue containing large malignant spindle cells, abortive osteoblasts and giant cells of the epulis type, such as are seen in sections of osteolytic sarcoma, are absent, although occasionally a blood vessel is seen, about which the malignant new bone may dispose itself in a more or less perithelial arrangement (fig. 82). Cartilage may occasionally be found in these new growths, but is never abundant,



Fig. 84 (P. N. 43060).—Roentgenogram and gross specimen of a case of sclerosing sarcoma occurring in a white man, aged 49. This patient was fed a madder diet on four consecutive days preceding amputation. The result is depicted in the gross specimen. The growth of the tumor at its periphery is shown by the dark areas, the recent osteoid substance having taken up the red dye and staining this portion only. The dye unfortunately had faded somewhat when the photograph was made, and is indicated by the arrows. The other dark spots are hemorrhage.

and its appearance in the sections is sufficiently atypical to justify the consideration of these cases as variants. These chondral variants of sclerosing sarcoma involve an earlier type of periosteum which still retains remnants of its perichondrial origin.

Histogenesis.—The evidence accumulated in this study leaves little doubt as to the source of this form of osteogenic sarcoma. The tumor takes its origin in the osteogenic layers of the periosteum which are particularly active in the formation of compact bone in the metaphyseal region of young adults and children in the pre-adolescent period. All the roentgenograms and the gross specimens emphasize the metaphyseal location and the subperiosteal origin of these tumors. The fact that this subperiosteal region is not active about the epiphysis after the age of 3 explains why these ends of the bone are never primarily involved by this neoplasm. The midshaft regions are rarely, if ever, involved in



Fig. 85 (P. N. 42852).—A chondral variant of sclerosing osteogenic sarcoma, showing the typical sclerosing roentgenographic picture. (Operation by Dr. Dean Lewis.)

young adults, because this same subperiosteal tissue has ceased to function as an active center of growth in this region of the bone after birth.

Evidently, therefore, a normal histogenetic transition from early connective tissue through osteoblasts to osseous formation, occurring at a rapid rate during the period of normal adolescent growth is necessary for the development of this type of osteoblastic, osteogenic sarcoma. This is borne out by the microscopic studies of this neoplasm, because the histology manifested repeats in all of its essentials the normal mode of the formation of membranous bone characterized by connective tissue, osteoblasts and osteoid spicules typical of these subperiosteal osteogenic

layers. It is also confirmed clinically by the restricted age period in which these growths occur and their sharply delimited localization in the skeleton.

The mechanism whereby this normal type of growth and histogenesis are transformed into the disorderly and malignant histologic cycle typical of this form of sarcoma is obscure. Although trauma is recorded in



Fig. 86 (P. N. 42852).—The gross specimen of the case shown in figure 85. The bulk of the tumor mass is lying beneath the periosteum; the marrow cavity has not been invaded.

50 per cent of these lesions, no direct connection can be traced between the immediate result of the injury and the subsequent malignant response. The problem is rendered even more difficult because the defensive reaction on the part of the body is unquestionably performed by means of a proliferation of the same type of membranous bone as occurs in the formation of the malignant process, and this normal

development occurs simultaneously with the malignant and abortive form of the same process (fig. 83).

The feeding of madder (a vegetable dye originally used by John Hunter to study the growth of bone) to patients with this form of sarcoma, has been carried out previous to operation, and the subsequently amputated specimens have been examined. The dye localized in the areas of new bone but stained the osteoid substance rather than the cells concerned in osteogenesis. It was therefore possible to confirm the fact that the tumor was arising subperiosteally, and its most actively



Fig. 87 (P. N. 42852).—Low power photomicrograph showing the lobular tumor mass ossifying beyond the cortex in the subperiosteal zone. (Same case as shown in figure 86.)

growing border was on the side of the periosteum rather than next to cortical bone, but the differentiation of the early malignant cells from embryonic cells of normal type concerned in the production of reactive bone was not accomplished (fig. 84).

Prognosis and Treatment.—Although the duration of the symptomatology is brief, averaging less than ten months, and the postoperative duration of life in fatal cases averages only fourteen months, the percentage of cures effected by radical operation is unusually great in this type of sarcoma. In sixty cases in which complete data were available, including follow-up study, extending over a period of five years

or more, there were sixteen cured patients living five years or longer. All these cures were effected by radical operation, amputation being performed when possible and radical resection in cases affecting the clavicle or rib. In all but two cases, the radical operation was instituted at once. In two of the living patients, however, there had been previous aspiration or exploration followed by amputation at an interval of weeks or months.

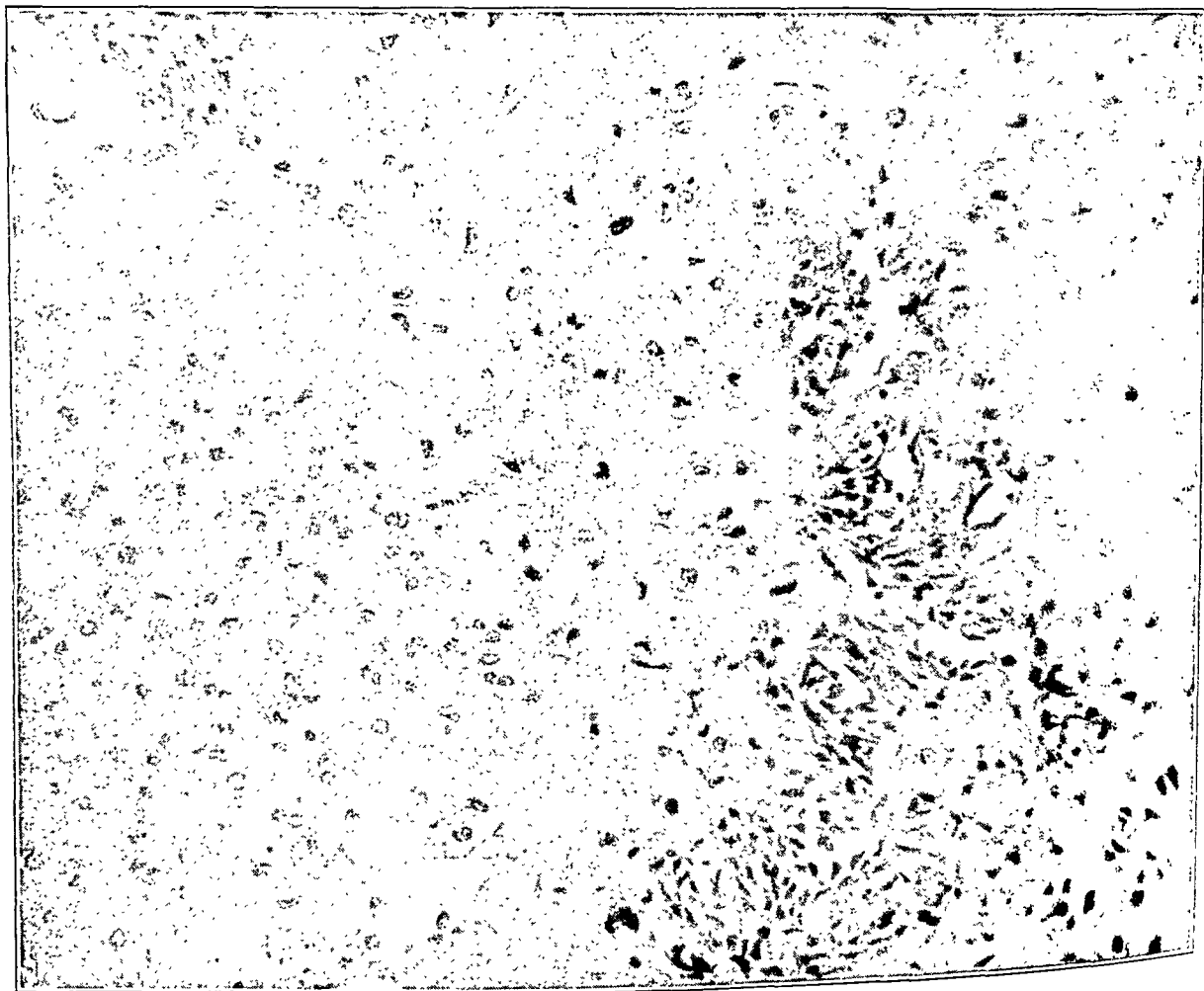


Fig. 88 (P. N. 42852).—High power photomicrograph showing a cartilaginous area undergoing conversion into an osteoid substance. (Same case as in figures 85 and 86.)

These data leave no question as to the procedure of choice in this type of sclerosing sarcoma of the bone. Radical amputation or resection should be performed at the earliest possible date, and if exploration is done this should be under the tourniquet. Frozen sections should be made with an immediate and competent pathologic report, and the operation proceeded with at once. If facilities for frozen section are

not available and consultation is required in the diagnosis, the roentgenograms and not the sections should be sent, as a diagnosis can usually be obtained roentgenologically without the necessity of exploration, if the proper authorities are consulted. This is the method advocated by Bloodgood.

Deep roentgen therapy does not result in cure in these cases and only restricts the rate of advance of the peripheral margin of the lesion. Two of the patients considered cured had received Coley's toxins in

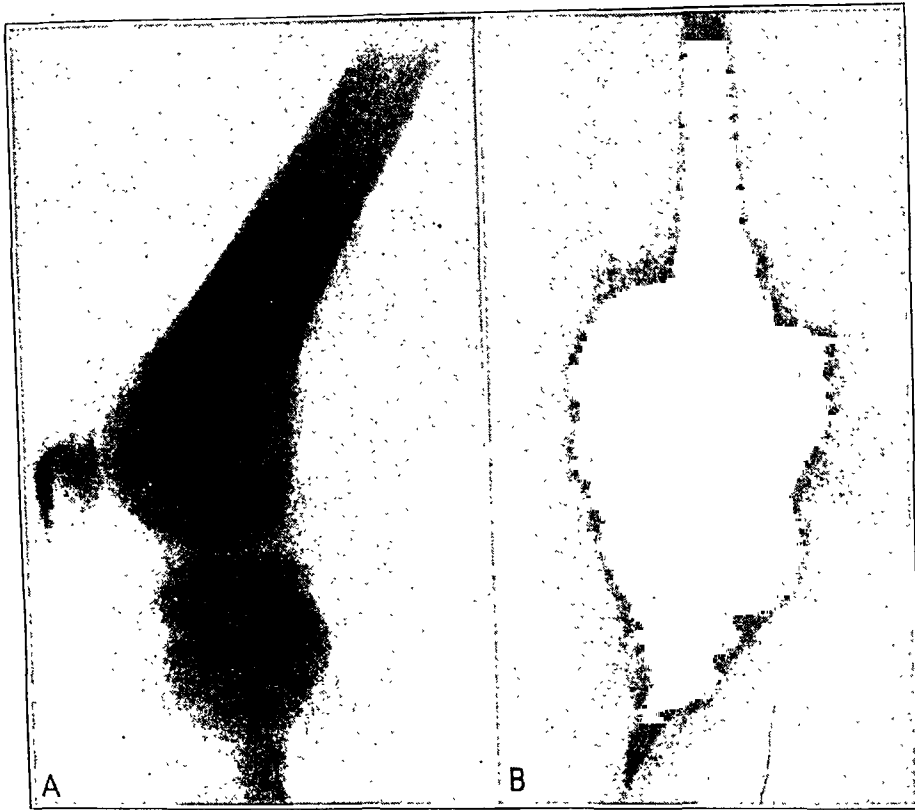


Fig. 89 (P. N. 37008).—A mixed round and spindle cell variant of sclerosing osteogenic sarcoma. *A* shows the roentgenogram before exploration. The tumor mass is seen arising subperiosteally, causing periosteal lipping and producing a cloudy extracortical shadow rather than the characteristic picture of sclerosis. *B* shows the roentgenogram taken three months after that of *A*. There had been four local operations and the tumor is now frankly sclerosing in appearance.

addition to radical operation. Three had also had the benefit of post-operative irradiation.

In regard to the prognosis, it is possible to state that in the patient with the sclerosing sarcoma of the bone, regardless of age, provided the lesion is situated where complete resection or amputation is possible, the chances of cure are more than 25 per cent, if primary radical

operation is performed. This probability of a cure becomes less the longer the duration of symptoms prior to operation and the greater the interval of time elapsing between an incomplete primary operation and radical treatment. It can also be stated that patients surviving radical operation after eighteen months, who show no signs of recurrence or metastases at that time, will, in all probability, remain free from disease.

This high percentage of five year cures in osteogenic sarcoma is unusual, and the better prognosis in patients with this sclerosing form depends on the state of differentiation of the malignant cells or osteoblasts which represents the apex of development in the derivation of bone from connective tissue. The better prognosis in these sarcomas

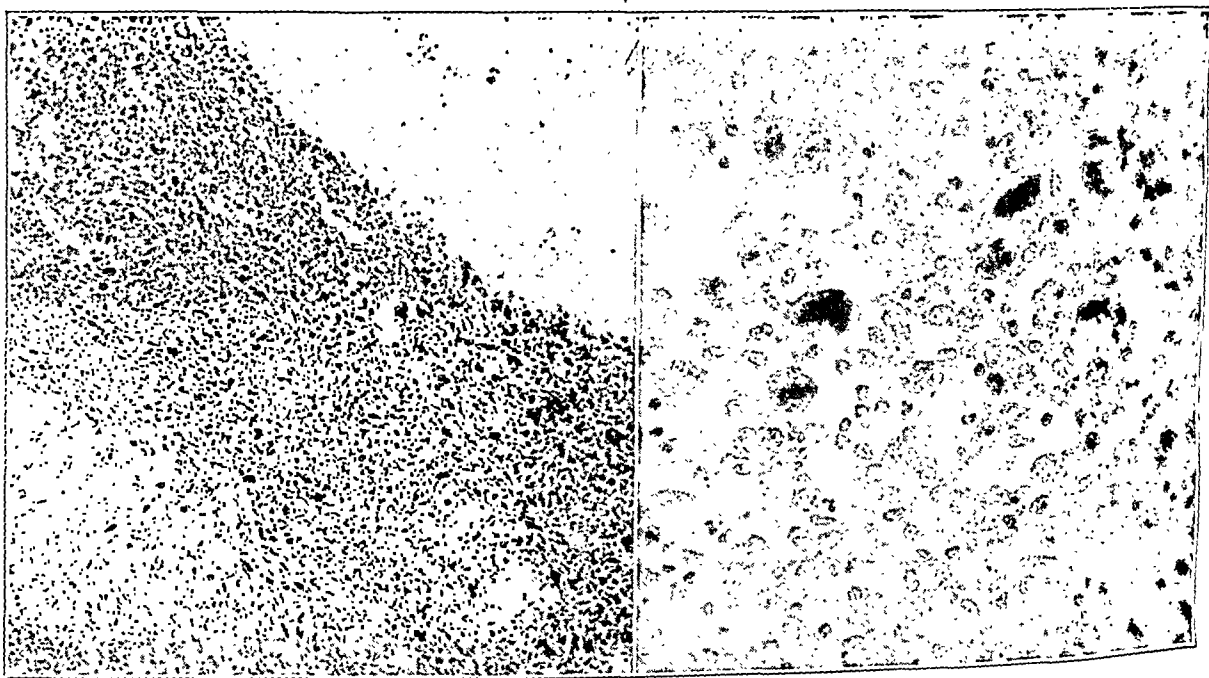


Fig. 90 (P. N. 37008).—Low and high power photomicrograph indicating the histologic structure of the tumor shown in figure 89. The tissue is very vascular, contains many abortive osteoblasts and resembles microscopically an osteolytic form of osteogenic sarcoma.

is in keeping with the general rule that the higher the state of differentiation in the neoplastic tissue, the less malignant is the clinical course.

VARIANTS OF THE SCLEROSING FORM OF OSTEOGENIC SARCOMA

While the predominant microscopic picture described for the sclerosing form of osteogenic sarcoma did not include cartilage or the malignant spindle cell with abortive osteoblasts, typical of the osteolytic type of sarcoma, cartilaginous tissue and a vascular tissue of malignant spindle and round cells may appear in periosteal sarcoma belonging to this main group.

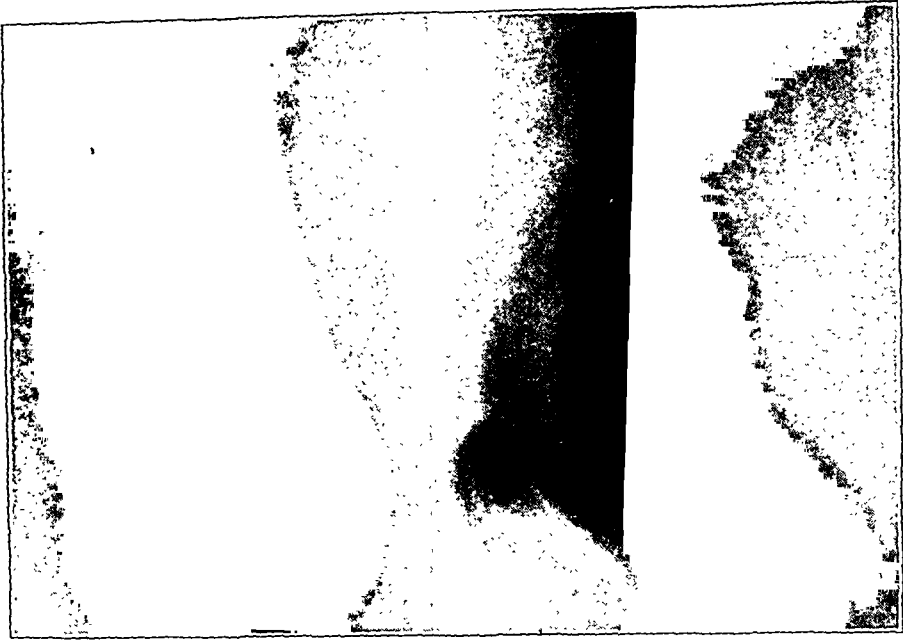


Fig. 91 (P. N. 27852).—A case of early sclerosing sarcoma classed as a mixed spindle and round cell variant. There is a characteristic roentgenographic appearance. The bulk of the tumor is subperiosteal and of a translucent appearance but secondary bone destruction has occurred in the marrow cavity.



Fig. 92 (P. N. 27852).—The gross specimen of the case shown in figure 91 which emphasizes the white, fibrous and osteoid substance of the tumor mass and the central hemorrhagic cavity opened up in cancellous bone which is typical for osteolytic sarcoma.

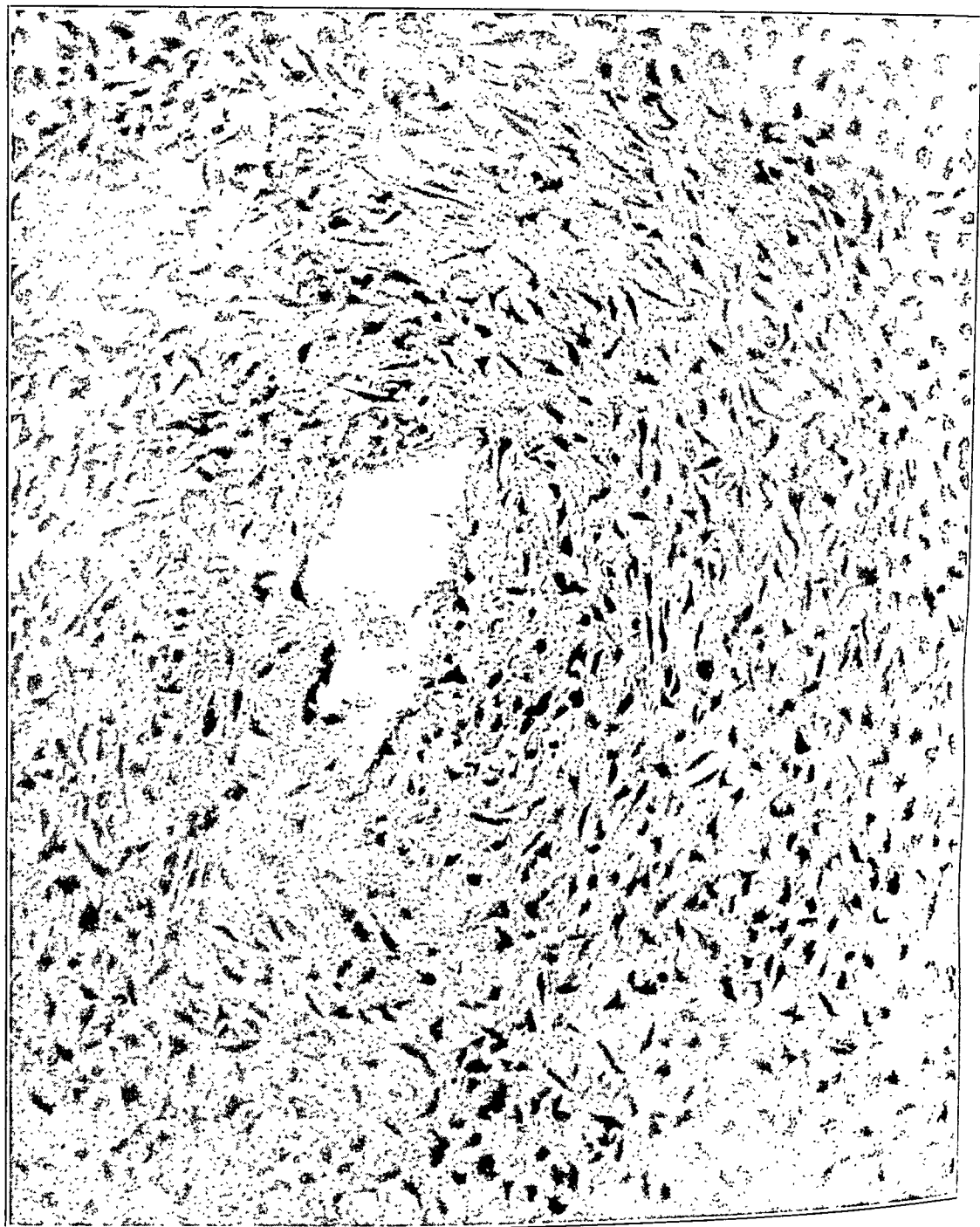


Fig. 93 (P. N. 27852).—The photomicrograph depicts spindle cells and early osteoblasts embedded in a pre-osteoid substance, indicating an early stage of ossification. (Same case illustrated in figures 91 and 92.)

About one case in five of the sclerosing form of sarcoma may show, under the microscope, small islands of cartilage being converted directly into an osteoid state. The presence of this cartilage is readily explained by the fact that the periosteal tissue from which the neoplasm arises is only a further stage in the development of the primitive perichondrium. Most of this periosteum, it is true, has lost the power to form cartilage at the time when these growths arise, but some of the more undiffer-



Fig. 94 (P. N. 28352).—Roentgenogram showing a fracture of the right ulna in a white man, aged 67, in which sclerosing sarcoma is arising in the callus. The fracture occurred one year previous to the symptoms of tumor formation. The patient died of metastases two and one-half years after amputation at the shoulder girdle.

entiated cells must persist and take part in the new growth. I do not believe that the chondral substance is to be accounted for on the basis of atavism or dedifferentiation on the part of portions of the periosteal tissue. From the standpoint of the clinician, the inclusion of small areas of cartilage in these growths is negligible. It affects in no way the roent-

genologic picture, nor is the prognosis influenced as far as can be determined from the clinical follow-up (figs. 85, 86, 87 and 88).

The mixed spindle and round cell variant of sclerosing, osteogenic sarcoma is worthy of more important consideration. It presents a predominantly bone-destructive appearance in the roentgenogram and coincides from a microscopic and prognostic standpoint with the osteolytic variety of osteogenic sarcoma. For this reason, in the tables it has been included with the osteolytic cases which are central in origin,

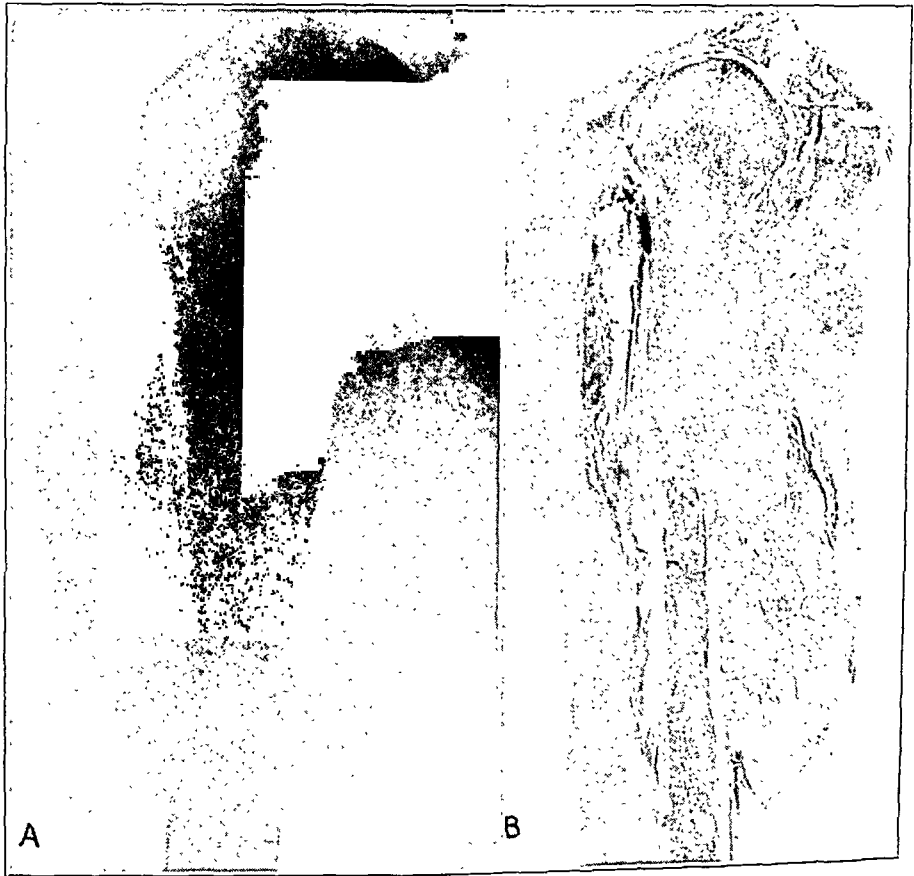


Fig. 95 (P. N. 36014).—A case of myositis ossificans undergoing secondary change into sclerosing osteogenic sarcoma in a white man, aged 28. *A*, taken in October, 1923, depicts the formation of new bone of a laminated character in the soft parts, typical of myositis ossificans traumatica, but in addition there is periosteal reaction indicating early malignancy. *B* shows the specimen amputated in July, 1926. The picture shows a fully developed sclerosing sarcoma which has infiltrated the marrow cavity.

although this variant itself must be conceded to be periosteal in its origin. There is no satisfactory way to classify this small group of lesions clinically (seven cases), since no matter how they are looked on they constitute a confusing exception. In the roentgenogram (figs. 89 and 91), they resemble a primary chondrosarcoma. In the gross and micro-

scopic specimens (figs. 90 and 92), they duplicate features of the osteolytic variety of tumor, and from a histogenetic standpoint they are closely allied with the sclerosing form (fig. 93). These tumors show an activity in primitive connective tissue of the periosteum, and although osteoid substance is produced that is midway between the osteolytic and sclerosing forms, the major portion of the tumor does not achieve a highly differentiated stage of osseous production.

Considering the twofold method of achieving bone in the skeleton, either from precartilaginous connective tissue, through cartilage to bone or from pre-osseous connective tissue directly to bone, it is readily understandable that a neoplasm exhibiting a highly differentiated state of ossification may retain remnants indicating a beginning in either the

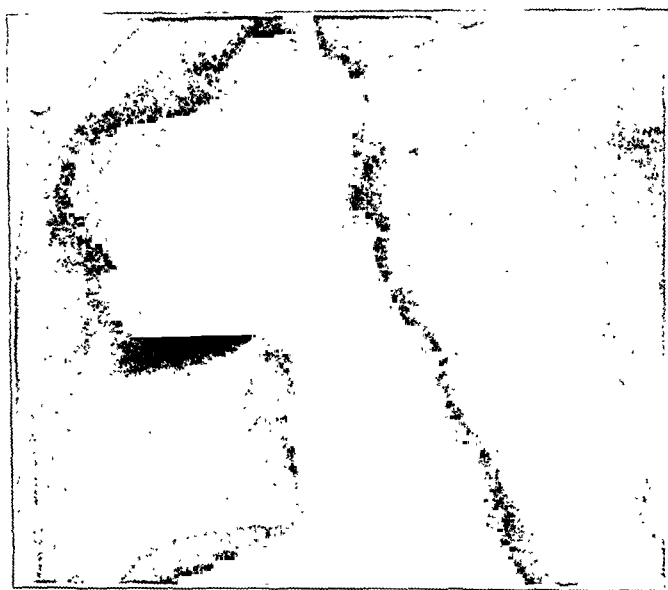


Fig. 96 (P. N. 36014).—Roentgenogram showing consolidation of the upper right side of the chest by tumor metastases, occurring in March, 1929, in the same case shown in figure 95.

more primitive precartilaginous or the pre-osseous state. On this basis, the areas of cartilage or mixed spindle and round cells found in sclerosing osteogenic sarcoma may be accounted for.

Secondary Sclerosing Sarcoma.—The clinical data just reviewed indicate that the usual sclerosing osteogenic sarcoma, whether typical or representing one of the variant forms described, arises *de novo* during the active period of growth of the skeleton. Practically all of the patients are between 15 and 35 years. There are, however, a few exceptions (four among seventy-eight cases), patients who are beyond the period of growth, and the inference is that the malignancy is secondary to an original primary and benign lesion.

This is definitely indicated by the data in one of the cases. In this instance, a white man, aged 67 (fig. 94), had fractured his right elbow one year previously. The roentgenogram showed a distinct ununited fracture with diffuse callous formation about the upper end of the ulna. In this callous formation a secondary malignant change occurred, and the patient died of metastases two and a half years after an amputation at the shoulder girdle.

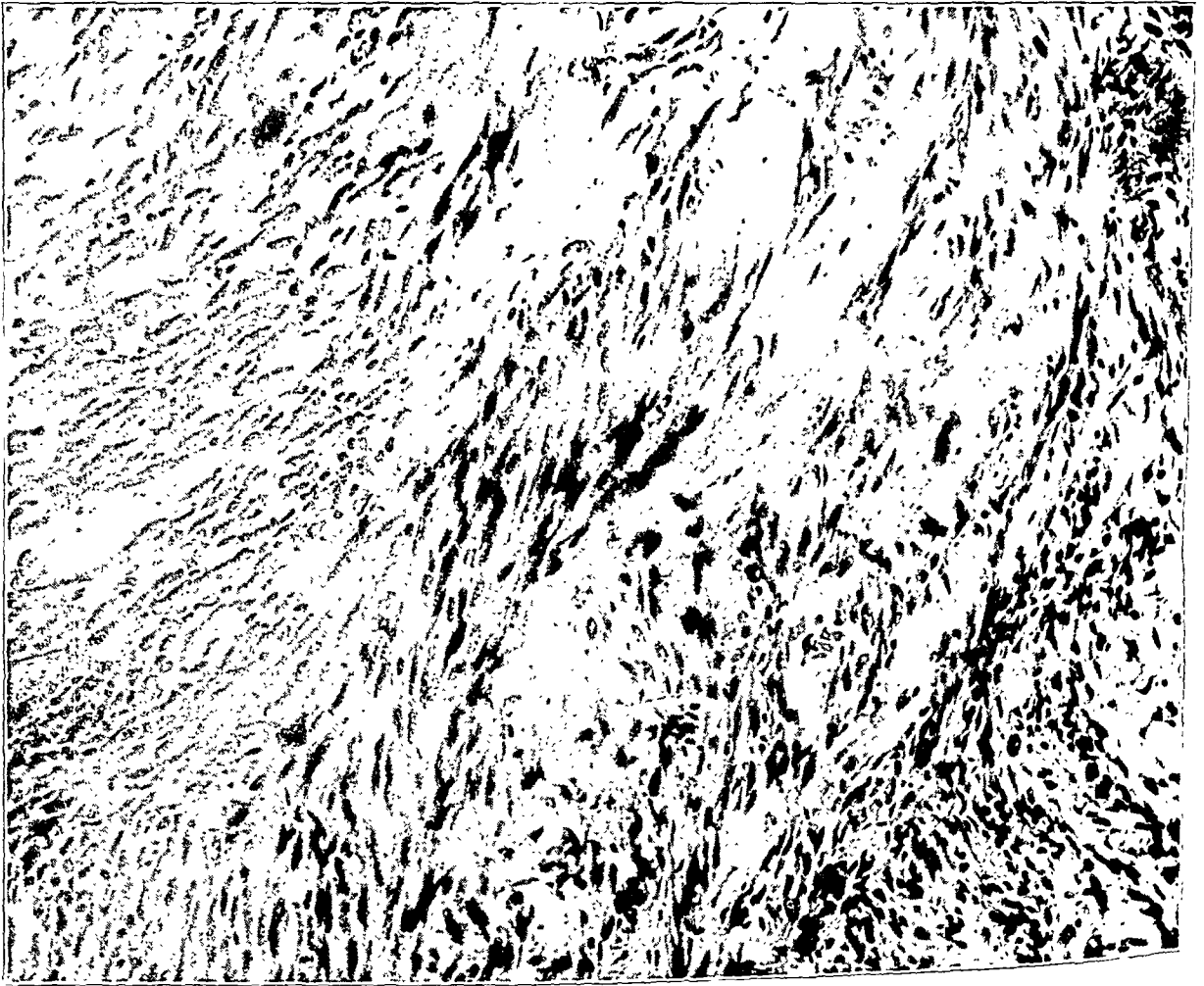


Fig. 97 (P. N. 36014).—Photomicrograph showing malignant new bone in the case illustrated in figures 95 and 96.

In another case, a white woman, aged 38, complained of acute pain in the left side of the chest which was more intense on coughing. A brace was applied to the chest, roentgen therapy was given, and the lesion became apparently better. A year later the symptoms recurred, and a roentgenogram revealed an osteogenic sarcoma arising over the fourth rib in the axillary line. Although the examination was performed elsewhere and an inquiry was not made in regard to trauma, the history

suggests that this was apparently another instance of secondary sarcoma arising in the callus of a fracture.

Two other instances of secondary sclerosing osteogenic sarcoma in patients 28 and 34 years of age, respectively, are recorded in the laboratory. Both of these arose in a previously benign myositis ossificans and are shown in the accompanying illustrations (figs. 95 to 99).

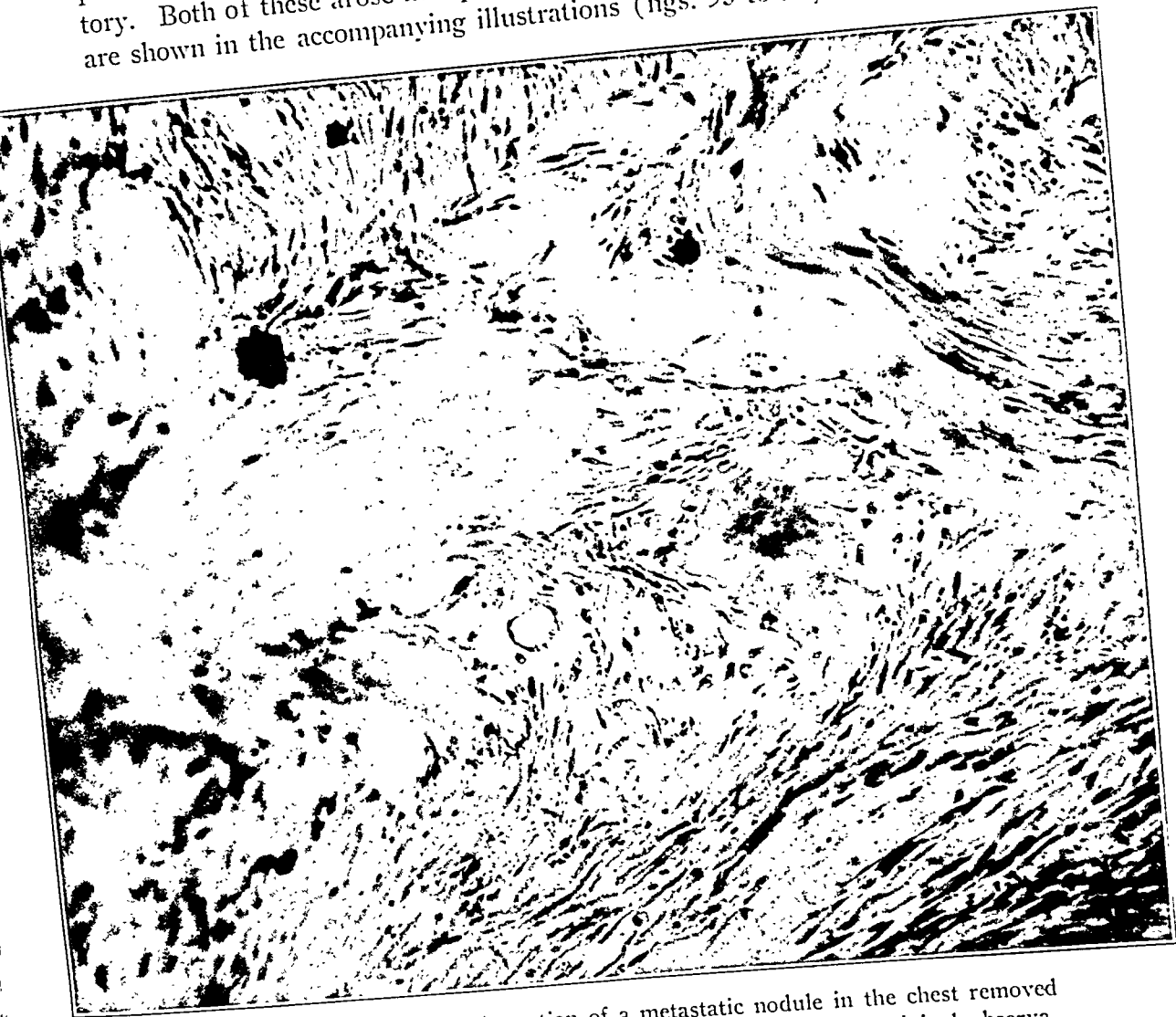


Fig. 98 (P. N. 36014).—A portion of a metastatic nodule in the chest removed at autopsy. The patient died in July, 1929, six years after the original observation. (Same case as shown in figures 95 to 97.)

These proved instances of sclerosing, osteogenic sarcoma arising secondarily to benign lesions are in keeping with the evidence studied in regard to the other forms of osteogenic sarcoma. Both chondrosarcoma and the osteolytic varieties may arise as primary or secondary lesions, and to the sclerosing form must also be ascribed such possibilities.

CONCLUSIONS CONCERNING THE FIBRO-OSSEOUS FORMS OF
OSTEOGENIC SARCOMA

In contrast to the chondral forms of osteogenic sarcoma, the fibro-osseous forms just discussed may achieve from the histogenetic standpoint a high degree of cellular differentiation, so that a relatively mature product of ossification represents the end-point of the series. This end-point, the sclerosing type of osteogenic sarcoma, is the least malignant of all the neoplasms discussed here and presents a fair degree



Fig. 99 (P. N. 27702).—A case of osteogenic sarcoma developing in myositis ossificans about the upper end of the fibula in a white woman, aged 34. *A*, taken in October, 1919, shows the ossifying periosteal mass with signs of malignant change. *B* shows the recurrent malignant growth in October, 1922, three years after a resection of the upper third of the fibula. This patient is living in 1931, eight years following an amputation for the recurrence. This case was reported by Paul (*ARCH. SURG.* 10:185 [Jan.] 1925).

of curability. From a microscopic standpoint, therefore, these tumors may be definitely graded, the more mature cell forms being the least malignant. As in the chondral forms of sarcoma, the age of the patient is also a factor in the degree of malignancy, and among the osteolytic types of the fibro-osseous group it has been shown that the patients who

are cured are usually adults; on etiologic grounds there is reason to believe that secondary malignant change rather than a primary sarcoma was present in these successfully treated lesions. In this respect the osteolytic type of sarcoma presents a form that closely parallels secondary chondromyxosarcoma. In the more highly differentiated sclerosing sarcoma, age is not a striking factor unless the secondary form of malignancy, which is rare in this group, is present.

Separation of these fibro-osseous sarcomas into separate histogenetic types and the placing of the chondral forms likewise on an individual pathologic basis bring out forcibly the relation of these sarcomas to the processes of osseous development. It can be concluded from the analysis herein presented that a different type of tumor is possible for each phase of the histogenesis of the bone, emphasizing in a forceful way that the origin of these growths is intimately connected with the developmental steps in osteogenesis.

TABLE 6.—*Results in One Hundred and Sixty Fibro-Osseous Sarcomas*

	Sclerosing	Osteolytic
Total.....	73	87
Lost.....	5	6
Total followed.....	68	81
Followed over five years.....	55	63
Well over five years.....	17	4
Per cent of five year cures.....	31	6

CONCLUSIONS AND CLINICAL APPLICATIONS

The separation of osteogenic sarcoma into separate forms based on the individual phases of osteogenesis involved is not a theoretical attempt to arrive at the etiology of sarcoma, but is a serious endeavor to comprehend the behavior of these growths in their clinical aspects, although it cannot be denied that this analysis sheds a decided light on the nature of the malignant process in bone.

In summarizing some of the more important conclusions derived from this study, it is therefore advantageous to focus attention on the outstanding clinical applications.

Significance of a Protracted History.—The current conception of the typical sarcomatous history met with in patients suffering with malignant disease of the bone is in need of definite revision. A youthful patient and a brief acute clinical course are not indispensable to the diagnosis, and it can no longer be claimed that a prolonged history and advanced age rule out this dread disease. It has been shown that there are definite types of osteogenic sarcoma which arise in adults who may give a story of a preceding trauma dating back two to twenty-five years.

These are cases of secondary chondromyxosarcoma arising at the site of an exostosis or benign central chondroma, the osteolytic sarcoma which arises centrally in adults with an obscure complaint at the site of the malignant change, or the secondary sclerosing forms following on myositis ossificans and in callus after fracture. In these cases the unusual clinical aspects can be explained on the basis of a sarcoma arising from a previously benign condition, which either harbors undifferentiated embryonic tissue or is the seat of a chronic unhealed lesion. The clinician, therefore, must be on the lookout for these secondary malignant forms of osteogenic tumors, which in the roentgenograms are central bone-destructive lesions of an infiltrative type (arising in a bone which gives evidence of a previous exostosis, an expansile deformity caused by central chondroma or an old unhealed site following infection or trauma) or invasive periosteal growths (following on Paget's osteitis deformans, myositis ossificans or callus formation). While these tumors are definitely sarcomatous, they offer a better prognosis than the primarily malignant osteogenic tumors, and in grading constitute a distinct group.

Interpretation of Roentgenograms.—The fundamental basis of interpreting lesions of the bone in the x-ray film is also in need of revision. There is too much overlap in the roentgenologic picture between benign and malignant conditions if one looks on the film as presenting only the configuration of the result of the disease process. It is necessary to pass beyond the reliance placed on mere configuration and analyze the film as a dynamic record of both normal osteogenesis and a malignant perversion of some phase of this osteogenesis. Thus, in primary chondrosarcoma occurring in youthful patients, the sites of bony tubercles and of tendinous attachments thereto must be looked on as a zone of active growth in which the osseous portion of the tubercle is in balance with the precartilaginous portion of the tendon. When both proliferate, producing an osseous pedicle in bone and a cartilaginous cap in the tendon, the normal is exaggerated but the balance is still maintained, and the lesion is a benign exostosis. When the primitive cartilaginous portion only proliferates as a translucent periosteal shadow, the lesion is a primary chondrosarcoma. When the equilibrium reached in the exostosis is overthrown at a later date in a similar manner by precartilaginous tissue, the result is a secondary chondrosarcoma. From a similar point of view areas of destruction about a persisting epiphyseal line in a youthful patient must be regarded in relation to the active growth zone at this point, and the possibility of a chondroblastic sarcoma considered. Throughout the growth period lesions of the metaphysis that escape beyond the cortical shell must be looked on with suspicion, and their relationship to sclerosing osteogenic sarcoma ascertained. The

osteolytic form of sarcoma must be thought of as a possibility when the cancellous bone in this metaphyseal region is involved by a destructive process, and a cavity in the bone opened up which escapes beyond the cortex. The coincidence of a separate type of osteogenic sarcoma with an individual zone of osseous development explains the variability of the roentgen finding in this group of neoplasms. The fact that osteogenic sarcoma may sometimes give rise to a central osteolytic lesion in the x-ray film, and in other instances sclerose the marrow cavity; that under certain conditions it may be predominantly a periosteal lesion, and again be predominantly central, emphasizes the necessity of interpreting the roentgenogram in relation to the phase of osteogenesis involved by the tumor rather than attributing these contrasting pictures to chance or to an indefinable complexity.

Coordination of Clinical and Pathologic Findings.—A more complete coordination between the clinical and pathologic picture is made possible by this factoring of the various forms of osteogenic sarcoma. The pathologic findings of giant cells in the central destructive forms of sarcoma of either the chondroblastic or osteolytic types need no longer be a source of confusion to the surgeon or the pathologist who understands that secondary invasion by the giant cells is to be expected as a subordinate phase to either cartilaginous proliferation in chondroblastic sarcoma or to the laying down of poorly formed osteoid substance among the large malignant spindle and round cells of osteolytic sarcoma. There is thus no need to try to stretch the conception of benign giant cell tumor to include these malignant phases that are in reality primarily sarcomatous.

The malignancy of chondromyxomatous tumors in which myxoma and actively proliferating early connective tissue predominate is on a surer footing when the idea that myxoma is a degeneration product of cartilage is abandoned and when this precartilaginous tissue inappropriately referred to as myxoma is viewed instead as the mother substance of these growths. It is also helpful to know by the same token that the cartilage in these growths is the result and not the progenitor of the myxomatous tissue.

The pleomorphic forms of osteoblasts scattered among osteoid substance and spindle cells without relation to spicule formation serve to set apart the production of malignant bone of sclerosing sarcoma and to differentiate it from normal reactive bone laid down in spicule formation in benign inflammatory conditions and osteitis fibrosa. The close relationship of the histology of this tumor to such normal osseous production at the same time gives a key to the better prognosis among patients with this sclerosing neoplasm as compared with sarcoma in bone of other forms.

Grading of Osteogenic Sarcoma.—For the first time a fairly reliable grading of the degree of malignancy of sarcomas of the osteogenic group is made possible, and the prognosis rendered more than a shrewd guess. The clinical aspects of the lesion, including the roentgenogram, may be used in conjunction with the microscopic picture to grade these neoplasms. When the most advantageous treatment is used, from 5 to 10 per cent of permanent cures is the base line. This is the minimum opportunity for escape from fatality whether the lesion is a chondromyxosarcoma, a chondroblastic sarcoma or an osteolytic sarcoma. From this minimum the chances of cure are increased fivefold, if the lesion arises as a secondary malignant change or if the tissue of origin is of the highly differentiated sclerosing form. The higher the age of the patient and the more protracted the clinical course, the more likelihood is there of a secondary and hence more benign type of sarcoma. This likelihood is strengthened when the roentgenogram shows evidence of a pre-existing exostosis or chondroma in a chondromyxosarcoma or a central bone-destructive growth of the osteolytic type in an adult over 30, and is confirmed when the microscopic picture shows a tumor in which myxoma and necrotic cartilage predominate, or when the tumor contains malignant spindle and round cells with giant cells indicative of the osteolytic type. In the sclerosing form the shaggy sun-ray picture in the x-ray film and the predominance of osteoblasts and osteoid substance under the microscope establishes the better prognosis.

Indications for Irradiation.—Deep roentgen and radium therapy have now taken their places as established methods of treatment in malignant disease, and the question of whether or not a neoplasm is histologically of a proved radiosensitive type is an extremely important consideration. Taken as a group, it is impossible to state whether or not the osteogenic sarcomas are or are not radiosensitive, and unless these tumors have been analyzed on a histogenetic basis, this matter cannot be decided. From the present study, however, it can be concluded that the forms of osteogenic sarcoma arising from precartilaginous connective tissue (chondromyxosarcoma) and cartilage (chondroblastic sarcoma) show definite evidence of being relatively radiosensitive, and those tumors of the fibro-osseous series are relatively radioresistant. This is in keeping with the general rule that all neoplasms arising in tissue of an undifferentiated embryonal type are prone to yield to radiotherapy, whereas those involving a more highly differentiated group of cell forms are usually refractory to this mode of treatment. At the present time, radium therapy has achieved better results than deep roentgen therapy in the chondral forms of sarcoma. A review of the cases in which cure has been obtained does not show any difference in the ultimate outcome of cases in which irradiation has been used preoperatively and those in which it has been used postoperatively.

It is important to emphasize, however, that in none of the forms of osteogenic sarcoma can it be proved that irradiation alone suffices for a permanent cure. When irradiation has been tried over a period of one month as the initial form of treatment without definite and striking results, surgical measures should be promptly instituted.

Etiology.—The relationship of tumors of the bone to various phases of osteogenesis herein set forth correlates the age of the patient and the site of the tumor characteristic of the individual forms of osteogenic sarcoma with the time and locality of normal histogenetic processes occurring in the various growth zones of the skeleton. That such a correlation is not the result of mere coincidence is demonstrated by the histologic composition of the neoplasm itself, which duplicates in epitome, although in a somewhat distorted manner, the normal order of developmental steps peculiar to the tissue from which it arises. It may be concluded, therefore, that a normal and active center of tissue differentiation constitutes a predisposing cause to the formation of tumor. This conception enlarges the insufficient embryonic theory of Cohnheim, recognizing that histogenesis in the tissue is not confined to the embryo, but occurs in all normal structures at various periods throughout life. This, however, does not detract from the veracity of the Cohnheim doctrine, for it has been shown in the secondary forms of osteogenic sarcoma that relatively undifferentiated tissue may be harbored in a benign neoplasm until late adult life, and affords independent of normal growth cycles the basis of subsequent tumor formation. Although a restricted age incidence and a characteristic localization is thus one of the fundamental attributes of a well defined neoplastic entity, a belated and less malignant tumor of the same histologic type may arise in more advanced age, as a secondary change to some benign growth.

An important corollary to this histogenetic conception of neoplasms is that the variety of etiologic factors proposed for malignancy—trauma, infection, chronic irritation, metabolic or endocrine imbalance, etc.—must be looked on as precipitating agents only for these new growths. The properties of the consequent neoplastic transformation are inherent in the tissue of origin rather than in the etiologic agent, and remain constant for a given tumor despite variability in the factors of causation. The developmental steps concerned in the construction and growth, in the maturity and eventual senescence of bodily tissues and organs from this standpoint constitute more fruitful fields for investigation into the nature of malignancy than do the various carcinogenic agents of a chemical or bacterial nature so diligently searched for in many laboratories.

normal in from six to twenty-four hours after induction of anesthesia in animals. The glycogen in the liver is depleted. Preliminary ligation of the veins of the liver prevents the rise in blood sugar, thus proving that the liver is a factor in absorption and detoxication. The alkali reserve remained normal. Like ether, tribromethanol causes a decrease of calcium in the blood. The p_H , according to Wymer, is decreased even for as long as twenty-four hours.

Margin of Safety: Kärber and Lendle showed that surgical anesthesia was obtained in rabbits by rectal administration of 0.35 Gm. per kilogram, whereas fatal doses of the drug are from 0.55 to 0.6 Gm. per kilogram of body weight. Therefore, it appears that the anesthetic dose is approximately 65 per cent of the fatal dose.

Effect of Repeated Use: Repeated administration of avertin over a long period of time produced no injury to the internal organs of animals. A dose of from 400 to 500 mg. per kilogram was given rectally to white mice on one hundred successive days with no deleterious effects on any of the abdominal viscera. Some of the animals became pregnant during this time and had healthy offspring. On the other hand, ether and chloroform were not nearly so well tolerated, the animals succumbing after a few tests.

CLINICAL APPLICATION

Preanesthetic Medication.—The general plan of preanesthetic technic among the German clinicians is relatively uniform. A cleansing enema, or a mild cathartic, is given the night before the operation. The patient is put on a liquid diet. Some somnifacient, such as dial or barbital, is given the evening before. The preoperative hypodermic injection of morphine-scopolamine or papaverine is given about one and one-half hours prior to the administration of tribromethanol. Martin elaborated the technic by advocating the administration of fractional doses of scopolamine and a morphine-narcotic meconate mixture with fractional doses of avertin, using age as a basis. He reported full narcosis in 96 per cent, the cases including all types of surgical procedures.

Preparation of Solution.—Tribromethanol is usually administered in a 2.5 per cent solution. The solid avertin is dissolved in warm water, the temperature of which does not exceed 104 F. The solution hydrolyzes at from 110 to 115 F., giving off hydrobromic acid and dibrom-acetaldehyde, which reacts distinctly acid to congo red.

By using avertin fluid the technic is simplified. The amount is measured in a Luer syringe or a graduated pipet, the average dose being about 0.1 Gm. per kilogram of body weight. Moerin stated that doses in excess of 0.15 Gm. per kilogram are too high for general use. He suggested giving a dose of 0.1 Gm. of avertin fluid per kilogram, and if the patient is sensitive to pain after fifteen minutes, an addition of 0.25

Gm. per kilogram is given. Various solvents such as physiologic solution of sodium chloride, 1 per cent salep mucilage, gum acacia or milk have been used; however, most authors agree that distilled water is least cumbersome and causes less intestinal irritation.

Dosage.—The dosage of tribromethanol has varied from 0.08 to 0.2 Gm. per kilogram of body weight. In using the solid avertin, doses as high as from 0.15 to 0.175 Gm. per kilogram have been given. However, the general dosage that can be regarded as safe is 0.125 Gm.

In using avertin fluid the dosage is less, 0.1 Gm. per kilogram corresponding to 0.125 of solid avertin. This has been proved clinically by Grossmann in a report of 215 cases. Most fatalities or excessive decreases in blood pressure have been noted only in those cases in which the dosage was in excess of 0.125 Gm. for avertin fluid and 0.150 Gm. for the solid avertin.

Sievers reported 1,200 cases in children who received from 0.125 to 0.150 Gm. per kilogram of body weight in a 3 per cent solution. No untoward effects were noted. If necessary, avertin was supplemented with a small amount of ether, as particularly advocated by Ebhardt and Anschütz.

Depth and Duration of Anesthesia.—The depth and duration of rectal administration of avertin vary greatly in different persons. Children show a marked tolerance to avertin, and, as previously stated, tolerate larger doses of the anesthetic. In administration of dosages based on weight, only 30 per cent of the children were completely anesthetized, while in adults given the same relative dosage, from 70 to 80 per cent were surgically anesthetized. The patient sleeps from three to five hours, depending on the type of patient and the dosage. No excitement stage has been noted by any of the German clinicians. Nausea and vomiting are extremely rare.

Dangers and Remedies.—The principal dangers in the use of tribromethanol anesthesia, aside from injections of a hydrolyzed solution, which causes irritation and slough of rectal mucosa, are respiratory and circulatory changes and impairment of the excretory organs.

Respiratory: Impairment of respiration due to the action on the respiratory center is the greatest danger of avertin fluid anesthesia. In case of impairment, carbon dioxide is most efficacious (Martin), and in mild cases of impairment, lobeline. This drug is effective; however, in grave respiratory embarrassment it has proved to be a failure.

Dressen reported a death occurring in a woman 68 years of age with a blood pressure of 220 systolic and 170 diastolic and with chronic nephritis. A radical operation for carcinoma mammae was contemplated. One-tenth gram per kilogram of body weight in a 2.5 per cent solution was given rectally. Five minutes after the beginning of the instillation, respirations ceased. The pulse was not palpable. Lobeline

and artificial respiration relieved the condition. Twenty-five minutes after the enema, the operation was begun, and the same collapse recurred. The remaining solution in the rectum was drawn off. Carbon dioxide and lobeline were ineffective, and the patient expired on the operating table. No autopsy was obtained.

In accordance with the experience of Killian, coramine "ciba" given intravenously up to 4 cc. exerted a marked stimulation of the rate of respiration, thereby bringing about a rapid awakening from avertin narcosis. Thus coramine proved to be the most valuable adjunct in combating respiratory and circulatory failure, presumably by its rapid action on the medulla oblongata.

Circulatory: Prophylactic administration of ephedrine is of value and proves very effective in those cases in which there is a marked drop in blood pressure. Pribram showed that thyroxine raises the blood pressure and shortens narcosis. In one case he administered 1 cc. of thyroxine to a patient whose blood pressure had fallen 70 mm. of mercury and in whom the pulse was not palpable. Thyroxine raised the blood pressure, and the patient was fully awake in two hours.

Urinary: Urinary complications are rare. Transient albuminuria, occasional erythrocytes and granular casts have been noted.

Kallmann reported the case of a healthy patient who was given 0.125 Gm. per kilogram for an Alexander-Adams operation. Barbitol, 0.5 Gm., was given the night before and repeated two hours before operation. As a preoperative hypodermic, 0.02 Gm. of pantopon was given. The patient expired seventeen and one-half hours after operation. Autopsy revealed fatty infiltration of liver cells. The urinary bladder was empty. The kidney showed fatty infiltration of the tubuli contorti. Kallmann assumed that damage to the kidney was caused by avertin. Death was probably due to the barbitol, pantopon and avertin preparation, which in the opinion of Anschütz is a faulty preparation.

Contraindications for the use of avertin are: 1. Severe liver damage. The matter of liver damage by avertin is still under discussion. Heinecke maintained that postoperative prophylactic feeding of dextrose makes avertin narcosis safe even in diseases of the liver. Cholecystectomy was done by Heinecke on a patient under avertin, aged 42 years, who had symptoms of common duct obstruction and severe jaundice over a period of fourteen years. The dose given was 0.15 Gm. per kilogram of body weight. The patient died on the fifth day with mania and an intense jaundice. Death could probably have been avoided by using a smaller dose and prophylactic preoperative administration of dextrose and insulin.

2. Severe kidney damage.

3. Chronic ileus with ensuing acidosis, dehydration and shock. If these adverse conditions can be overcome by administration of dextrose

and fluids intravenously, avertin can be given with impunity; however, in reduced dosages.

4. Severe cachexia due to malignant growths. In these cases the dosage must be reduced.

According to Anschütz, the relative danger and mortality of the different anesthetics in the hands of experienced men are as follows:

- (a) 1 death in 10,000 avertin (Specht)
- (b) 1 death in 5,112 ether (Gurlt)
- (c) 1 death in 2,075 chloroform (Schmieden and Sebening)
- (d) 1 death in 2,524 spinal (Strauss)
- (e) 1 death in 343 splanchnic (Mecker)

CLINICAL INVESTIGATION OF AVERTIN FLUID AND TECHNIC OF ADMINISTRATION

In November, 1930, we began the use of avertin fluid for anesthesia at the Deaconess Hospital. Our original technic was the one used for solid avertin, gathered from German surgical reports. Since that time we have almost completely revised our original method, including pre-operative and postoperative care for the patient who is to receive rectal administration of avertin fluid.

Preparation of Patient.—In the afternoon preceding the day of operation the patient is weighed and given a cleansing enema, either a soap suds or a salt solution enema. At bedtime some type of somnifacient, as dial, is administered. We do not advocate the use of narcotics on the evening preceding operation unless the patient has considerable pain. Oral hygiene is effected by the use of a mouth wash. As a preanesthetic medication given by hypodermic injection one and one-half hours before operation, we have used $\frac{1}{3}$ grain (22 mg.) of pantopium hydrochloride¹ and $\frac{1}{100}$ grain (0.6 mg.) of scopolamine as a routine measure in patients over the ages of 17 to 18 years. In persons below these ages, the dosage is decreased to $\frac{1}{6}$ grain (11 mg.) of pantopium hydrochloride and $\frac{1}{200}$ grain (0.3 mg.) of scopolamine. No preoperative narcotic is given to children under 10 years of age. In all preanesthetic medications given by hypodermic injection, we have used scopolamine in ampule form, and we have found this preparation to be the most stable and to cause less depression of the respiratory center. Naturally, the preoperative medication did not produce the same effects in all persons. Some stated that they were only slightly drowsy, while the greater number showed no appreciable changes. However, we did not

1. This preparation was purchased under the brand name of Pantopon. Since this work was done the Council on Pharmacy and Chemistry has issued a report rejecting Pantopon (J. A. M. A. 97:1001 [Oct. 3] 1931) for conflict with certain of its rules.

use this as a guide for either increasing or decreasing the dose of avertin fluid. In all cases we administered the same minimum dose of 0.1 Gm. per kilogram of body weight.

Preparation of Solutions.—In all our cases we used avertin in amylene hydrate, or avertin fluid, as it is called commercially. Distilled water sufficient to make a 2.5 per cent solution in an Erlenmeyer flask is heated on an asbestos plate over a gas flame to a temperature between 100 and 104 F. The computed amount of avertin fluid according to weight is measured with a graduated syringe, or pipet, and added to the heated distilled water. By thorough shaking, the avertin fluid disseminates itself, and the result is a clear homogeneous fluid.

One or two cubic centimeters is placed in a small container, and a drop of congo red is added. The mixture remains pink, or neutral, to congo red. We have not, up to the present time, had to discard any of the mixtures due to positive reaction to the indicator. We found that avertin fluid is much more readily miscible in heated distilled water than in nonheated water. The solution is administered immediately after mixing.

Dosage.—Persons over 17 years of age were given 1 cc. or 0.1 Gm. of avertin fluid per kilogram of body weight, while in children the dosage varied from 0.125 to 0.150 Gm. per kilogram of body weight. Distilled water is added to make a 2.5 per cent solution. In obese persons, in severe cachexia and dehydration and in severe liver damage, as advocated by German clinicians, we reduced the dose to 0.08 or 0.09 Gm. per kilogram, depending on the condition of the patient.

Method of Administration.—The blood pressure apparatus is placed on the patient's arm before instillation of the solution, and the blood pressure and the pulse are recorded. The solution is administered one-half hour before operation, in bed, with the patient lying on his left side and in a moderate Trendelenburg position. This is effected by turning up the foot of the bed, or by placing pillows under the hips of the patient. A soft rubber catheter is inserted into the rectum for about 3 or 4 inches. A long-necked bulb syringe is placed into the end of the catheter, and the solution is allowed to gravitate into the rectum. In those cases in which the solution did not gravitate, we have used the bulb syringe, or blown the solution through the funnel. The length of time used for the instillation was usually from five to eight minutes. The remainder of the solution in the catheter is forced into the rectum as previously described, and the catheter is withdrawn while blowing into the funnel. We have not encountered any loss of solution.

Supplementary Anesthesia.—Local anesthetic was used in but one case with good results.

In those cases in which the patient reacted, we have used nitrous oxide exclusively with extremely favorable results. The amount of nitrous oxide used was negligible in most cases, except when the operations lasted longer than two hours. We do not advocate additional doses of avertin solution because it entails too much inconvenience when the patient is draped, sterile, on the operating table. We agree with most American writers that in those cases in which full anesthesia is not obtained with avertin solution, a tangible anesthetic, preferably nitrous oxide in our experience, be used. We were never forced to supplement with ether to obtain relaxation in those cases in which avertin solution did not produce complete surgical anesthesia, providing 0.1 Gm. per kilogram was given.

In ten cases we attempted to prolong the effects of avertin fluid by preliminary administration of 3 grains (0.19 gm.) of sodium amytal by mouth, two hours before operation. We observed that in those cases the sodium amytal diminished the depth of anesthesia otherwise obtained with avertin fluid alone.

Management During and After Anesthesia.—From the time the solution is injected until complete recovery, the patient is under careful supervision. The anesthetic is given in the room, and the patient is taken to the operating room about twenty-five minutes after the beginning of the instillation. The anesthetist remains with the patient until after the operation, at which time an experienced nurse stays at his side. We do not advocate the insertion of an airway until the patient reaches the operating room, since the absorption is not sufficient to cause abolition of the pharyngeal reflex, and this is manifested by considerable coughing. Respiratory embarrassment early after instillation has not been noted by us. After the patient has been prepared on the operating table, the airway is inserted, and all patients have well tolerated the procedure. In those cases in which there is an excessive drop in blood pressure, and if it does not rise after the incision, we advocate the use of ephedrine sulphate; after the use of this drug we have noted an almost immediate rise. Diligent watching of the patient and frequent blood pressure readings should be particularly stressed.

After operation the patient is brought back to his room and the pharyngeal airway is allowed to remain in place until he attempts to expel it himself. A subcutaneous hyperdermoclysis of 1,000 cc. of physiologic solution of sodium chloride is given immediately, which procedure we have found to shorten narcosis from one to one and one-half hours. Intravenous medication, unless deemed necessary for combating surgical shock, has not been given. Pantopium hydrochloride, $\frac{1}{3}$ or $\frac{1}{6}$ grain, depending on the age of the patient, is administered by hypodermic injection as a routine measure for pain and restlessness, and we have found that only a few doses are required, because the anes-

thesia seems to allay pain for the first twelve hours. On awakening, the patient is given fluids by mouth, in quantities as are comfortably tolerated. Many patients have taken orange juice and broth on the day of operation.

Mortality.—In our series of cases there have been two mortalities, not directly attributable to avertin anesthesia. In both cases the patients came to the operating room in a dehydrated condition. They illustrate why many authors exclude avertin in cases of chronic ileus, on account of the existing dehydration with acidosis.

CASE 1.—A patient with a ruptured gastric ulcer was given 0.1 Gm. of avertin per kilogram of body weight. The clinical history was that of an ulcer of rather acute onset. The ulcer, as nearly as could be ascertained, had been perforated approximately twenty-eight hours, during which time there was coffee-ground vomitus. Examination revealed a well developed man, in severe shock, and pale; the extremities were cold and clammy. The abdomen had boardlike rigidity. On laparotomy, a large ruptured gastric ulcer was found on the lesser curvature. The stomach contents, including food, and digested blood clots were found in the abdominal cavity. The patient never rallied from the anesthesia and apparently succumbed to overwhelming shock and peritonitis, two hours after operation. No autopsy was performed.

CASE 2.—A patient with intestinal obstruction and annular carcinoma of the sigmoid had symptoms of obstruction of five days' duration. He had been vomiting two days. The abdomen was markedly distended. No results were obtained with enemas or cathartics. On examinations, the pupils were found to be unequal; they reacted sluggishly to light but reacted in accommodation. A diagnosis of syphilitic heart disease was made. The blood pressure reading was 135 systolic and 80 diastolic. On laparotomy, a large annular carcinoma was found at the first portion of the sigmoid, and the large and small bowel were markedly distended. A right pararectal colostomy was done. The patient, on returning from the operating room, was cyanotic; the pulse was weak and fast. Stimulants were administered intravenously, but to no avail. Two hours and thirty-five minutes after operation, the patient died.

Postmortem examination revealed the cause of death as follows: syphilitic endocarditis and myocarditis, chronic syphilitic aortitis and aspiration pneumonia.

OBSERVATIONS

Induction.—The patients who received rectal administration of avertin fluid seemed to fall into a normal sleep. Narcosis took place in from five to twelve minutes, and in all cases we attempted to use that much time for instillation so that on removal of the catheter the patient would not be stimulated. Some patients continued to talk during the instillation, but within a few minutes the tongue would become thick, and later the response would be only a mumbling. The head and arms relaxed very soon, and the patient appeared as if in a deep slumber.

Vomiting persisted in the case of intestinal obstruction, even after instillation of the anesthetic and during the entire operation. The patient expired. Any other type of anesthesia would have affected the

patient in the same way. The aspiration of some of the vomitus probably accounts for the aspiration pneumonia and death after circulatory failure.

Pharyngeal reflexes are lost in from twenty to twenty-five minutes. Responses to skin stimuli are lost in approximately twenty-five minutes after instillation; however, some patients reacted slightly after the initial incision was made. This proved to be an embarrassment in operations on the skin, such as excision of varicose veins and perineorrhaphy. The pupils contracted in about ten minutes but reacted to light. In the greater number of cases the pupils dilated to half the maximum after skin incision or peritoneal stimulation; the respiratory volume was increased. Muscular relaxation for laparotomy was excellent, even in those cases in which full surgical anesthesia was not obtained.

Duration of Anesthesia; Recovery.—Narcosis with avertin fluid ranges from three to five hours. One patient with secondary anemia slept eight hours. We noted that approximately 20 per cent of our patients showed restlessness on awakening; however, this has been successfully controlled with a mixture of opium alkaloids. The remainder of the patients awoke as if from a natural sleep. In not a few instances the patients inquired whether they had been operated on. Pain seemed to be allayed the first eight to twelve hours. We are convinced that by elimination of the psychic shock, by the administration of a basic anesthesia such as avertin fluid, the recovery is markedly shortened. The early return to normal physiologic function of the vital organs by the intake of nourishment by mouth is a point that we consider paramount for early recoveries.

Coramine "ciba" given intravenously or intramuscularly up to 4 cc. shortened narcosis from 40 to 50 per cent. In a few instances after injection of coramine "ciba," the patients awoke within one hour.

Circulatory Effects.—There is an initial drop in blood pressure, of about 10 to 15 mm. of mercury, which soon rises to the normal level and remains there. In a few cases the blood pressure during operation has dropped 30 to 40 mm.; the administration of ephedrine sulphate readily brought the reading up to the normal level. A marked pallor, however only transient, was shown by some patients. This phenomenon may be what some writers termed vasomotor depression. The pulse did not show any appreciable changes either in volume or in rate per minute.

A patient with a marked secondary anemia, some poikilocytosis, anisocytosis and a hemoglobin of 45 per cent (Dare) was given avertin fluid. The narcosis was extremely deep, and the patient did not react until after eight hours, even though 700 cc. of 10 per cent dextrose solution was given intravenously. No ill effects were noted; the blood cells and hemoglobin, in fact, were increased two days after operation.

Blood counts after operation showed results comparable to any other type of anesthesia. Waters and Muehlberger reported that no consistent or significant changes occur in the blood chemistry. The rise in blood sugar with avertin fluid is less than in other types of anesthetics.

Respiratory Effects.—The respiratory rate per minute generally remained the same. The volume per minute of inspired and expired air was decreased about one-third. In the presence of an acute respiratory infection, avertin fluid should not be given. A patient developed an acute respiratory infection during the night, and avertin fluid was given the following morning. From the beginning of narcosis the patient coughed severely, was cyanotic and appeared asphyxiated; an airway was not tolerated. Carbon dioxide, oxygen, ephedrine and caffeine were given, with a subcutaneous injection of physiologic solution of sodium chloride. The narcosis was shortened to one hour; the operation was not performed. We have found that about 5 per cent of the patients who have had avertin fluid developed a cough on the second or third day. This phenomenon we attribute to the exhalation of amylene hydrate through the alveolar walls, thus acting as an irritant to the mucosa of the throat. This is readily controlled by codeine sulphate.

Gastro-Intestinal Effects.—Nausea is extremely rare, and vomiting is uncommon, excepting in those cases in which there was excessive manipulation of the gallbladder, its ducts, the duodenum and the stomach. Even in those cases in which vomiting occurred, the patients had only one or two emeses as compared to incessant vomiting, even for days, after operations in which inhalation anesthesia was used. The patients, in most cases, took liquids in abundance on the day of operation. Only one case of bleeding from the rectum, in a patient who had had hemorrhoids, came to our attention. In no other case have we noted any subjective symptomatology. A proctoscopic examination has not been done.

Genito-Urinary Effects.—The urinary changes postoperatively are comparable to those in any other type of anesthesia. Urinary suppression was not noted. In five cases erythrocytes appeared in the urine on the second day, and on repeated analyses was found to be only a transient phenomenon. In three cases hyaline casts appeared in the urine; a trace of albumin had been noted preoperatively. In five cases leukocytes appeared postoperatively. In the remainder of the cases the changes were not significant.

Central Nervous System; Psychic Effects.—In none of the patients who received avertin fluid by rectum have we noted any excitement stage immediately after instillation. By the combination with scopolamine we dispensed completely with the psychic shock and the aftermath of a terrifying experience. Approximately 25 per cent of the patients

showed restlessness on awakening; the administration of $\frac{1}{3}$ grain of pantopium hydrochloride controlled this successfully at the onset. The patient awakens as if from a normal sleep. Postoperative psychoses have not been encountered.

SUMMARY

Avertin fluid given rectally to a patient with a preliminary administration of dial, pantopium hydrochloride and scopolamine leads to a natural sleep with complete surgical anesthesia in from 83 to 88 per cent of the cases, including all types of surgery. The psychic shock is completely eliminated.

In emergency cases with only an opium alkaloid preparation and scopolamine, surgical anesthesia was obtained in 75 per cent of the cases. In the remainder of the cases only a small amount of nitrous oxide was used and then only intermittently. We were never forced to use ether to obtain relaxation. The absence of headache and nausea and the rarity of vomiting are assets distinctive for this type of anesthesia.

Several hours of sleep after operation is very beneficial, and after the patient awakens, pain seems to be allayed the first ten to twelve hours.

Intravenous injection of coramine "ciba" shortens the duration of sleep without interfering with the stage of analgesia.

Early ingestion of liquids and nourishment by mouth after the patient awakens assures early restoration of physiologic function of the vital organs.

Narcosis is deeper and longer in the anemic and in the fasting patient.

Ephedrine sulphate readily controls any eventual fall in the blood pressure.

Antidotes, if needed, are carbon dioxide with an excess of oxygen and subcutaneous or intravenous salt solution and coramine "ciba" up to 4 or 5 cc.

Ill effects have not come to our attention. In acute respiratory infections, avertin fluid should not be given. Contraindications are severe kidney and liver damage. Smaller doses must be given to cachectic, very obese persons and to those with chronic ileus.

Hyperdermoclysis of 1,000 cc. saline solution immediately after operation restores blood volume and shortens narcosis from one to one and one-half hours.

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FORTY-SEVENTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Open Reduction in Congenital Dislocation of the Hip.—Putti and Zanolì¹ discussed the technic for arthrotomy in reduction of congenital dislocation of the hip. The indications for, and results of, open reduction were not considered in this article. During the thirty years, 1899-1930, 2,994 patients with congenital dislocation of the hip had been treated at the Rizzoli Institute, of which 94, or 3.1 per cent, required open or bloody reductions. Open reductions were done when bloodless reduction failed, or when dislocation recurred after changing the first cast, and in 15 patients of advanced age on whom closed reduction was not attempted. The general principle followed in operating was a gentle reposition or recomposition of the joint. All bone spicules and abnormal chondral formations in the acetabulum were carefully

This Report of Progress is based on a review of 215 articles selected from 629 titles dealing with orthopedic surgery appearing in the medical literature between July 4, 1931, and Dec. 5, 1931, supplemented by a few selected articles of older date. Only those papers that seem to represent progress have been selected for review.

1. Putti, V., and Zanolì, R.: *Chir. d. org. di movimento* 16:1 (May) 1931.

removed, the integrity of component parts of the skeleton being rigorously respected. Finally, the femoral head was replaced under an enclosed roof.

Putti's incision was similar to the Smith-Petersen approach, except that he cut through the belly of the tensor muscle and about from 1 to 2 cm. of the gluteus medius belly. To avoid shock, all patients received abundant amounts of alkalis and dextrose for several days preoperatively and for one week postoperatively. The operation was done on an orthopedic table with the legs in traction and perineal countertraction. The steps of the operation were as follows: skin incision, division of the iliotibial tract, incision through the proximal portions of the tensor fascia femoris and gluteus medius muscles and exposure of the capsule covering the femoral head. The incision was then carried through the deep fascia beneath the tensor and vastus externus muscles with ligation of the artery and of two veins found in it. Then by retracting the sartorius mesially, the capsular isthmus was exposed. An incision was made into the capsule overlying the epiphysis. Codivilla's isthmus dilater was now introduced. If possible, the isthmus was dilated sufficiently to admit the epiphysis, otherwise it was incised longitudinally. The acetabulum was inspected, and irregularities of the chondral surface were removed. If the round ligament was thickened or redundant, it was excised, as Putti felt that this might be a large factor in preventing a stable reduction. After the capsular adhesions to the femoral head were carefully freed, reduction was obtained by one of three methods. In relatively young patients, by traction the head was brought down opposite the acetabulum, and then by internal rotation of the leg reduction followed. In older patients, Putti frequently separated the insertion of the iliopsoas muscle from the lesser trochanter with a periosteal elevator, then covered the wound with sterile dressings, and carried out the Paci maneuver. Because the anterior part of the capsule had been cut, not infrequently the femoral head went backward beneath the gluteal muscles, and reduction could not be obtained. If this method did not succeed, the Codivilla hip lever was engaged between the head and the acetabulum, and with forward pressure on the handle of the lever and simultaneous gentle abduction, hyperextension and finally internal rotation of the leg, reduction was accomplished. Care was taken to avoid chondral or osseous damage to the femoral head.

If reduction was obtained by the Paci maneuver, the leg was fixed in the first position of Lorenz—twenty-five patients in the series. If, on the other hand, either of the two other procedures was used, the leg was fixed in plaster in the first position of Lange, that is, hyperextended, internally rotated and abducted about 45 degrees—fifty-two patients in the series.

In the younger patients who were treated in the Lorenz position, the first cast was kept on for one and one-half months; then the leg was gradually internally rotated, and a second cast applied, which was left on for a maximum period of three or four months postoperatively. In the case of patients treated in the Lange position, fixation in plaster was maintained for two or three months unless the patient was 8 years or older, in which case the plaster was removed after one month. Following removal of casts, physiotherapy and exercises were begun with continuous traction at night.

Seventy-eight cases were reported, including ten bilateral reductions with description of the operative findings. End-results were not stated. Summarizing, Putti found that abnormalities in shape and disproportion in size of the femoral head and acetabulum, adhesion of the capsule to the femoral head and constriction of the isthmus in capsule were the primary factors preventing bloodless reduction. Secondly, abnormalities of the round ligament and shortened pelvic muscles were determining factors. Putti did not advocate tenotomy of the adductor muscles.

[ED. NOTE.—This excellent article merits careful reading. Of necessity, many points of importance have been omitted in the abstract. Putti's vast experience and proficiency in handling congenital dislocation of the hip is emphasized by the low percentage of open reductions required in 2,994 cases.]

VITAMINS AND CALCIUM METABOLISM

Antirachitic Potency of Cow's Milk.—Hess and his co-workers² studied the antirachitic potency of milk from cows that had been fed irradiated yeast or viosterol. They found that such milk had a high antirachitic potency. In cases in which rickets was present, calcification was brought about within a month by giving this type of milk. Feeding of irradiated yeast to the cows gave rise to a more potent milk than feeding of viosterol, and it seemed to function automatically.

DISTURBANCES OF BONE DEVELOPMENT AND OSTEITIS FIBROSA

Disturbances of Bone Development.—The atraumatic patella partita was generally classified according to whether the line of division was horizontal, vertical or oblique. In each case the two segments lay in one plane, side by side. Paas³ reproduced roentgenograms in a case in which the two segments lay one on top of the other, a certain gliding being apparently possible between them. Other evidences of distur-

2. Hess, A. F.; Lewis, J. M.; MacLeod, F. L., and Thomas, B. H.: Antirachitic Potency of Milk of Cows Fed Irradiated Yeast or Ergosterol: Clinical Test, J. A. M. A. **97**:370 (Aug. 8) 1931.

3. Paas, H. R.: Arch. f. klin. Chir. **165**:322 (May 15) 1931.

bances in ossification of the entire skeletal system were present; the femoral heads were flat and broad, and the author interpreted these as evidence of an old Legg-Perthes' disease. He was of the opinion that two factors were concerned in the production of the syndrome; first, a primary anomalous embryonal center of ossification, and, second, mechanical strain, the result of a deformed hip joint and a knock knee.

In a family of thirteen members, Henninger⁴ found that seven displayed multiple cartilaginous exostoses, while the others were of small stature. The hereditary aspect was marked, as it was in the other forty families whose genealogies had been published. The lesion occurring in the chondro-osteogenic tissue was a dominant characteristic and transmitted as such. Defect of the lower end of the ulna, dislocation of the radial head, synostosis of the forearm or leg bones and genu valgum were typical findings. Elongation of the lower end of the ulna occurred in one case.

Parathyroidectomy.—Walton⁵ performed parathyroidectomy on four patients suffering from diffuse osteitis fibrosa. The tumor could not be palpated in any patient on clinical examination; it arose in every case in connection with the inferior parathyroid. The tumor tended to gravitate downward, either between the sternum and the clavicle or behind the trachea, depending on whether it was originally situated in front of or behind the thyroid fascia. In one patient a small tumor lying in front of the thyroid fascia was removed without benefit to the patient. It proved on microscopic examination to be a thyroid adenoma. A few days later a second operation was performed. After the thyroid gland had been retracted forward, the thyroid fascia was incised, and a tumor, the size of a plum, was discovered lying immediately in front of the second and third dorsal vertebrae. Walton thought that the explanation of why a parathyroid tumor had been sought for unsuccessfully in a few cases of osteitis fibrosa was that it lay hidden behind the thyroid fascia.

These four patients had been under the care of Dr. Hunter, who reported the results obtained by parathyroidectomy and likewise summarized the results obtained in all the published cases of osteitis fibrosa in which operation had been performed. Hunter, after reviewing all of the evidence, stated conclusively that diffuse osteitis fibrosa was caused by hyperparathyroidism, usually the sequel of a hyperplasia of one or more of the parathyroid glands.

[ED. NOTE.—The evidence grows stronger that parathyroid tumors play a very important part in the production of diffuse osteitis fibrosa.

4. Henninger, H.: *Deutsche Ztschr. f. Chir.* **232**:666 (Aug. 24) 1931.

5. Walton, A. J.: *Brit. J. Surg.* **19**:285 (Oct.) 1931.

The failure to palpate the tumor is well recognized by those interested in these cases as a common finding, and is not a contraindication to operation.]

Osteogenesis Imperfecta.—Stevenson and Cuthbertson⁶ described the pedigree tables of four families, one or more of whose members had suffered from bone fragility, blue sclerae, otosclerosis or liability to dislocations and sprains. Metabolic studies revealed definitely diminished retention of calcium phosphorus and magnesium in two children so affected. There did not appear to be any marked deviation of these minerals from the normal excretory paths in the two children and in two adults studied. The concentration of calcium and phosphorus in the blood was normal. Viosterol and cod liver oil had no specific effect on the condition.

Sorrentino⁷ reported the macroscopic and microscopic findings in osteogenesis imperfecta in a new-born child who died shortly following birth. There were six fractures, three of the frontal bone, two in the femur and one in the right humerus, and an incomplete fracture of the right elbow. Macroscopically, there was massive callus formation showing evidence of absorption and healing. The blood showed lymphocytosis, associated with an anemia. The roentgenograms showed thinning of the cranial bones and of the cortex of the long bones, with atypical calcification and abnormally large medullary cavities. The epiphyseal areas and ossification centers were normal. Generally there was a dysplasia of cortical bone.

All internal secreting glands appeared normal except the thymus, which weighed one tenth of normal weight, 2.5 Gm., and was abnormally small. Histologically, there was intralobular and extralobular sclerosis with a lymphoid degeneration and atrophy of epithelioid elements. The author referred to Frontalli, who had claimed that the development of the thymus in utero played a rôle in the process of ossification of the skeleton.

TUMORS

Synovial Membrane Tumors.—Twenty-nine cases of synovial membrane tumors were recorded in the literature. Faulkner⁸ described two personally observed cases in the present article. Twenty-five tumors had occurred in the knee; the remainder were in the ankle. The tumors were sarcomatous in nature, but the degree of malignancy varied greatly. In the twenty-nine cases there was a mortality of 14 per cent with loss of limb in 14 per cent, and a cure in 72 per cent. Sixteen patients retained good joint function, and in five the joint was resected. In the author's cases postoperative radiation was carried out with good results.

6. Stevenson, G. H., and Cuthbertson, D. P.: *Lancet* 2:782 (Oct. 10) 1931.

7. Sorrentino, C.: *Pediatrics* 39:625 (June 15) 1931.

8. Faulkner, D. M.: *Surg., Gynec. & Obst.* 53:189 (Aug.) 1931.

The symptoms were those of a loose body in the joint, and the diagnosis of a pedunculated synovial tumor was arrived at only at operation.

Benign Neoplasms of the Knee.—Eichbaum⁹ reported three cases of this rather rare group of tumors. The first was a papillary angiofibroma. It apparently arose truly from vascular tissue. Its papillary character was explained as a result of its unrestrained growth in the joint space. The other two tumors belonged to the group variously named "xanthosarcoma," "giant cell sarcoma," etc. The author took the interesting point of view that features of these tumors (hitherto considered as part of the basic picture) such as the cholesterol deposits, pigment deposits and inflammatory cells were the result of processes not truly part of the tumor itself. He pointed out that analogous giant cell tumors of tendon sheaths might lack the cholesterol infiltration. Incidentally, in one of his tumors arising from the internal meniscus, the appearance was that of a "lipoid foreign body granuloma" formed about needles of fat crystals. This type of reaction was different from the true xanthomatic giant cell sarcoma.

The tumors were benign blastomas arising from mesenchymal tissue.

[ED. NOTE.—It has been emphasized by others and pointed out here again by Eichbaum that the name xanthoma is a misnomer.]

Carcinoma in Osteomyelitis.—Benedict¹⁰ found that, of 2,400 patients with osteomyelitis treated at the Massachusetts General Hospital, 12 developed carcinoma in the sinus tract. Two of these patients were observed and studied by the author. Both had osteomyelitis of long standing, one of the femur, the other of the tibia, and both were cured by amputation.

The disease might be present at the mouth of the sinus, or might not be discovered until the depth of the sinus tract was reached. Although carcinoma in osteomyelitis was rare, the possibility of its occurrence should be borne in mind so that the diagnosis might be established by biopsy, or possibly by roentgen examination.

TUBERCULOSIS

Diagnosis of Tuberculosis of Bones and Joints.—Milgram¹¹ studied 142 cases of tuberculosis of bones, joints and bursae with proved diagnosis of tuberculosis on pathologic examination of tissue. Of these, 55, or 38.7 per cent, were not diagnosed as tuberculosis clinically. In 29.5 per cent, the onset of the disease was sudden. The variability of clinical signs was so great that no comparative analysis could be made of them.

9. Eichbaum, Franz: Beitr. z. klin. Chir. **152**:184 (April 29) 1931.

10. Benedict, E. B.: Surg., Gynec. & Obst. **53**:1 (July) 1931.

11. Milgram, J. E.: Diagnostic Inaccuracy in Tuberculosis of Bone, Joint and Bursa, J. A. M. A. **97**:232 (July 25) 1931.

The lesion was monarticular or local in character in 67.3 per cent of the cases. There were ten cases of tuberculosis of the diaphysis of the bone, in all of which the correct diagnosis was not suspected. Roentgen examination was of no aid or misleading in 37.3 per cent. Tuberculin tests were done in 103 cases; 20 of these were negative. A further check of these 20 cases with both human and bovine tuberculin gave a positive reaction in 8. The author felt that a carefully controlled repeated intradermal tuberculin test, if negative, was the most valuable of the simple diagnostic tests in tuberculosis. The author urged the more widespread use of cultures, guinea-pig inoculation and biopsy of tissue carefully chosen from the joint thought to be tuberculous.

Skin Sensitivity to Tuberculin.—Hough¹² made a study of a thousand consecutive orthopedic cases tested with human and bovine tuberculin. The series was divided into three groups. In the first group, those cases that clinically showed no form of tuberculosis, 89 per cent of the tests were negative; 5.2 per cent were positive with both human and bovine tuberculin, 4.4 per cent were positive with bovine but negative with human tuberculin and 1.6 per cent were positive with human but negative with bovine tuberculin.

In the second group, comprised of those cases that clinically showed some form of tuberculosis, 10.4 per cent of the tests were negative; 58.5 per cent were positive with both human and bovine tuberculin, 23.4 per cent were positive with bovine and negative with human tuberculin and 7.8 per cent were positive with human but negative with bovine tuberculin.

In the third group, consisting of cases of proved tuberculosis, 60 per cent showed a positive reaction to both human and bovine tuberculin; 33.3 per cent, a positive reaction to bovine but a negative reaction to human tuberculin, and 7 per cent (one case), a negative reaction to both.

Conclusions were that unless both human and bovine tuberculin were used, a definite number of positive results would be missed. If it could be assumed that the skin reaction to tuberculin was specific for the type of tuberculin used, the incidence of bovine tuberculosis in orthopedic cases was about three times as frequent as the human type.

[ED. NOTE.—These articles serve to emphasize the importance of exhausting all possible means for making a correct diagnosis in cases in which tuberculosis of the joint is suspected. Many series of statistics on tuberculosis must be accepted with considerable reserve because of the inaccuracies in diagnosis.]

Tuberculosis of the Sacro-Iliac Joint.—Parker¹³ stated that tuberculosis of the sacro-iliac joint was a rare condition, and that it was essen-

12. Hough, G. DeN., Jr.: *New England J. Med.* **205**:437 (Aug. 27) 1931.

13. Parker, G. L.: *New England J. Med.* **205**:573 (Sept. 17) 1931.

tially a disease of young adults. Of nine hundred patients admitted to the Lakeville Sanatorium during a period of five and one-half years, only twenty had tuberculosis of the sacro-iliac joint; fourteen were in males and six in females. Twenty case histories were given. From a study of the case histories it appeared that seven patients died, four were listed as being in poor condition, five were fairly well off and only one was in good condition, and in this case the tuberculous nature of the disease was not proved. The condition of the three remaining patients was unknown.

Tuberculosis of the Spine.—Madame Dejerine-Sorrel's researches seemed to show that operative treatment of Pott's paraplegia was inadvisable, because when the symptoms developed early, recovery was the rule when the patient was kept recumbent, and when the symptoms developed late in the disease, progressive and incurable paralysis, leading to a fatal termination, was inevitable. Girdlestone¹⁴ was strongly opposed to this view. In the past ten years he had operated on twelve occasions, with a varying technic. The rationale of his operation was, first, to relieve pressure on the cord, either by a costotransversectomy or a laminectomy, or both, and, second, to increase the stability of the spine by a bone graft. In most cases the operative intervention had been completed in one stage, but sometimes a laminectomy and a graft had been done first at one operation and costotransversectomy later.

Of the twelve patients, one has been operated on too recently for review. There were two deaths, both in late and clearly almost hopeless cases, one within twenty-four hours of shock, and the other four years later of coma. Of the remaining nine patients, four recovered partially and five completely. Two of the four patients who had recovered partially were still progressing and seemed likely to recover completely.

Girdlestone described in detail his technic and his case records.

[ED. NOTE.—The author's results are contrary to those generally reported in this country. He has had a large experience, however, and this expression of opinion merits further study of the question.]

POLIOMYELITIS

Epidemiology.—Aycock¹⁵ discussed the widespread immunity to poliomyelitis, which he believed due in many cases to subclinical infection with the disease virus. He disagreed with the belief that adult immunity could arise spontaneously without the action of an antigen. Data were offered as fairly conclusive evidence that adult immunity.

14. Girdlestone, G. R.: Brit. J. Surg. **19**:121 (July) 1931.

15. Aycock, W. L.: Immunity in Virus Disease, J. A. M. A. **97**:1199 (Oct. 24) 1931.

whether accompanied by any recognizable manifestations of the disease or not, was a specific, acquired immunity and not a maturation phenomenon. Reexposure was suggested as an important factor in the permanence of immunity.

Experimental.—Jungeblut¹⁶ demonstrated apparent allergic phenomena in poliomyelitis. Temperature studies were made on convalescent monkeys reinoculated with the original virus strain from five to eighteen months after the cessation of acute symptoms. Instead of the usual five to seven days afebrile incubation period, an almost immediate fever response was obtained of from three to five degrees by the end of two hours. Tests with monkeys previously vaccinated by subcutaneous intraperitoneal and intrathecal routes gave delayed responses midway between those of late convalescent monkeys and normal controls. Heat-killed virus emulsion was given intracutaneously in twenty-seven persons who had had poliomyelitis. No febrile reactions were noted, but there was local allergic redness and swelling of the skin which increased from the fifth to the twenty-fourth hour. The author found a preponderance of positive reactions among normal adults as compared with younger children. The author felt that the test was not sufficiently developed as yet to warrant its clinical application.

Serum Therapy.—Shaw and his co-workers¹⁷ reviewed 104 cases of poliomyelitis in which treatment was given in a single hospital from July to December, 1930, and discussed the value of serum therapy. Fifty-three patients were treated before the onset of paralysis, and 83.4 per cent showed no permanent paralysis. Thirty-nine patients were treated in the acute stage but after paralysis had set in. Of these, 23.1 per cent showed no permanent muscle involvement. In both these groups it was the older patients that showed the most permanent involvement. These figures were not considered conclusive, but were thought to be additional evidence of the value of serum therapy. Both human convalescent and hyperimmunized animal serum was used, and of these the latter type seemed more effective.

Lichtenstein¹⁸ believed that, despite the apparent value of convalescent serum in poliomyelitis of monkeys, its evaluation in human beings continued to be difficult. The problem of controls complicated judgment.

The first group reported consisted of sixty-nine cases of poliomyelitis in which treatment with serum was used after the appearance of paralysis. In thirty-two of these, the paralysis continued to increase. Twenty of the patients died, seven within twenty-four hours. This mor-

16. Jungeblut, C. W.: J. Exper. Med. **53**:159, 1931.

17. Shaw, E. B.; Thelander, H. E., and Limper, M. A.: Treatment of Poliomyelitis: Results in Series of 104 Cases, J. A. M. A. **97**:1620 (Nov. 28) 1931.

18. Lichtenstein, A.: Ztschr. f. Kinderh. **51**:39 (May 18, 1931).

tality corresponded to the Swedish figures of the 1905 and 1911 epidemics. The second group reported consisted of thirty-eight "preparalytic" cases of presumable poliomyelitis in which spinal fluid changes were positive. In fifteen of these thirty-eight, although convalescent serum was used, pareses developed subsequently. In seven of this fifteen, the paralysis vanished completely in time. One patient died of respiratory paralysis despite the administration of serum previously. In a third group of twenty "preparalytic" cases no serum was given; none of the patients developed paralysis. Of these nine, five completely recovered, leaving but four cases of paralysis in the original group of twenty.

It was difficult to evaluate the therapeutic efficiency of convalescent serum, but in cases in which it was used early, especially if meningitic symptoms were marked, its administration seemed to be indicated.

Fairbrother and Morgan¹⁹ obtained an antiviral serum of great activity against the poliomyelitis virus by the intramuscular inoculation of the living virus in two horses. Two other horses, however, failed to respond. Apparently some horses would, and others would not, produce an antiviral serum, and there was no means of ascertaining without trial whether any particular horse was likely to develop an antiviral serum.

[ED. NOTE.—These reports on serum therapy show a somewhat diversified point of view. The fact remains that, at least in this country at present, human convalescent serum is felt to be the best early treatment. If serum from animals can be obtained that will be as efficient or more so, its widespread adoption will be certain.]

ARTHRITIS

Agglutination Reaction.—Nicholls and Stainsby²⁰ found that the serum of patients suffering from atrophic arthritis gave a strong specific agglutination reaction with a strain of streptococci recovered from the blood and joints of patients with atrophic arthritis. They were able to establish a close antigenic relationship between this strain of streptococci and the hemolytic streptococci in scarlet fever and erysipelas. They believed that atrophic arthritis could be differentiated from hypertrophic arthritis, gout and gonorrheal arthritis by this reaction. This agglutination test, supplemented by the sedimentation reaction, afforded a useful aid in determining the activity of the disease.

Surgical Therapy.—Meyerding,²¹ in a well illustrated article, discussed the relief of certain of the deformities occurring in chronic

19. Fairbrother, R. W., and Morgan, W. T. J.: *Lancet* 2:584 (Sept. 12) 1931.

20. Nicholls, Edith E., and Stainsby, W. J.: *Streptococcal Agglutinins in Rheumatoid Arthritis: Preliminary Report*, J. A. M. A. 97:1146 (Oct. 17) 1931.

21. Meyerding, H. W.: *Surgical Treatment of Chronic Arthritis*, J. A. M. A. 97:751 (Sept. 12) 1931.

arthritis. The prevention of deformities in the early stages of the disease by splints and guarded exercise was emphasized. Synovectomy in selected cases improved function and lessened pain in cases with persistent swelling of the larger joints. Little could be expected, however, from this procedure when extensive injury to the cartilage had occurred. The correction of long-standing contractures was accomplished by manipulation, capsulotomy, tenotomy and osteotomy. Certain painful monarticular deformities were relieved by arthrodesis. Arthroplasties gave the most gratifying results in the elbow joint, although good results were obtained in ankylosed joints in the lower extremity and in the fingers.

Sympathetic Ganglionectomy and Ramisection for Chronic Arthritis.—Moore²² reported the result of sympathetic ganglionectomy and ramisection on himself after he had suffered four years from arthritis with fairly extensive local vascular disturbance. Marked improvement occurred with an apparent arrest of the progress of the disease both in the upper and lower extremities.

[ED. NOTE.—Some of the editors have observed later progression of the disease after a period of temporary improvement following sympathetic ganglionectomy. We would caution against too great enthusiasm.]

SPINAL LESIONS

Schmorl's Bodies.—Brandes²³ reviewed the literature (German) on these lesions in the vertebral bodies and quoted Schmorl, who believed that in most cases they possessed no clinical significance. The author reported twelve cases, reproducing the roentgenograms, and observed that while there was no doubt that the bodies might be of traumatic origin in certain cases, as in some patients with vertebral fractures, and others with simply severe back strains, yet in the majority of cases no definite traumatic etiology could be adduced. In some cases pain accompanied the presence of Schmorl's bodies. In others, the findings were accidental. After an injury it was necessary to take roentgenograms in two planes if the nodules were to be seen. They were only roentgenologically visible when outlined by sclerosis. The medicolegal aspects were suggested. Interpretation of the importance of these nodules would be difficult.

Hypertrophy of Ligamenta Flava.—Towne and Reichert²⁴ reported two cases of hypertrophy of the ligamenta flava which had produced

22. Moore, J. R.: Results of Sympathetic Ganglionectomy and Ramisection for Chronic Arthritis: Personal Experiences of a Physician, J. A. M. A. **97**:172 (July 18) 1931.

23. Brandes, K.: Deutsche Ztschr. f. Chir. **231**:361 (May 7) 1931.

24. Towne, E. B., and Reichert, F. L.: Ann. Surg. **94**:327 (Sept.) 1931.

compression of the lumbosacral roots with resulting symptoms of cauda equina pressure. The condition had not been previously reported. The cause was not known, and the pathologic process was simple hypertrophy of the ligament demonstrable by injection of iodized poppy seed oil 40 per cent. There were also changes in the spinal fluid. Both were relieved by operation, that is, removal of the hypertrophic ligament.

CIRCULATORY DISORDERS

Differentiation of Peripheral Arterial Spasm and Occlusion.—Scott and Morton²⁵ described a test to differentiate vasoconstrictor spasm from occlusion in the common vascular diseases of the extremities. With the patient lying down, the temperature of the toes and soles of the feet was taken every five minutes with a thermocouple. After the level of surface temperature had been established, the posterior tibial nerve was blocked just below the internal malleolus with 1 per cent procaine hydrochloride. Surface temperatures were then recorded every five minutes. If there was a marked rise in temperature, usually to 30.5 C. or more, a vasoconstrictor spasm was the cause of the local circulatory deficiency. If there was very little or no change in temperature, vasoconstrictor spasm played no rôle in the deficient circulation.

Surface Temperatures.—Morton and Scott²⁶ believed that surface temperature recorded without reference to normal standards was of little value. The actual use of skin temperature in degrees did not tell as much as the relationship of this to the minimum and maximum normal levels. This relationship gave an indication of the degree of vasoconstriction or occlusion. Consequently, normal vasodilation levels were determined by the use of general anesthetics, spinal anesthesia and by local block of peripheral nerve trunks. Corrections were made for room temperature. The lower limits of vasodilatation as determined by skin temperature were found to be 31.5 C. for general or spinal anesthesia and 30.5 C. for conduction block anesthesia.

25. Scott, W. J. M., and Morton, J. J.: *Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients*, J. A. M. A. **97**:1212 (Oct. 24) 1931.

26. Morton, J. J., and Scott, J. M.: *New England J. Med.* **204**:955 (May 7) 1931.

(To be Concluded)

EXPERIMENTAL STUDY OF BONE REPAIR

EFFECT OF THYROPARATHYROIDECTOMY AND OF THE ADMINISTRATION OF PARATHORMONE

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The observed relationship of the parathyroid glands to calcium and phosphorus metabolism and of vitamin D to rickets and osteomalacia and the possible interrelationship between the parathyroid glands and vitamin D have served as the stimulus for a great amount of experimental and clinical investigation of the factors that govern or may influence bone growth and bone repair after injury. In addition to the question of analyzing the causes that may operate to delay union or bone repair, there is the question of the possibility of accelerated repair, which can be more intelligently approached as the physiologic mechanisms of ossification become better understood. In the older literature there are several reports that the partial or complete absence of the parathyroids causes a lessened deposition of calcium in the osteoid tissues during periods of growth or repair; for example, that in growing rats and dogs after partial parathyroidectomy the deposit of enamel, dentine, bone and callus is poorer in calcium than that in the normal animal (Erdheim,¹ Iselin,² Toyofuku,³ Canal⁴ and Morel⁵). The isolation of parathormone has enabled experimental hyperfunction of the parathyroids to be studied as well as hypofunction, and as a consequence there is a considerable amount of newer literature dealing with the relation of the parathyroid glands to bone growth and repair. Some of this newer literature may be referred to briefly.

HYPOFUNCTION OF THE PARATHYROIDS

Ghiron,⁶ in 1924, reported experiments in which he performed partial parathyroidectomy in dogs, and noted arrested growth of the bones.

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1. Erdheim, J.: *Frankfurt. Ztschr. f. Path.* 8:175, 293, 1911.

2. Iselin, H.: *Deutsche Ztschr. f. Chir.* 18:494, 1908.

3. Toyofuku: *Frankfurt. Ztschr. f. Path.* 7:249, 1911.

4. Canal: *Gazz. d. osp.* 30:977, 1909.

5. Morel: *Compt. rend. Soc. de biol.* 68:749, 1911.

6. Ghiron, V.: *Arch. ital. di chir.* 10:238, 1924.

Ogawa,⁷ in 1925, reported that cauterization of the parathyroids in rats having fractures of the femur resulted in a callus less in weight, ash and calcium content than that in controls when examined at twenty days. Dieterich⁸ reported in 1925 that, while parathyroidectomy delayed callus formation, roentgen and histologic examination proved the process essentially normal otherwise. Hammett,⁹ in 1927, reported that parathyroidectomy in the rat results in bones of lower calcium and phosphorus and of a higher magnesium percentage than normal for the age. Chandler,¹⁰ however, in 1927 reported experiments in which he fractured the forelimbs in a series of parathyroidectomized rats and compared the histologic findings with those of litter mate controls at various intervals of time, and stated that he found no significant differences in healing between the two groups. Ravdin and Morrison,¹¹ in 1928, reported that thyroparathyroidectomy in dogs having fractures retarded ossification, but did not prevent union. Ross,¹² in 1928, reported experiments on cats in which the radius and ulna were fractured and varying degrees of parathyroid deficiency produced. He concluded that the removal of two parathyroids does not delay the union of fractures, but that the removal of three parathyroids delays bony union for as long as from four to five weeks. Speed and Rider,¹³ in 1930, reported observations on the healing of fractures in thyroparathyroidectomized dogs in which tetany was controlled by calcium lactate. They noted delayed union and defective calcification of the callus.

HYPERFUNCTION OF THE PARATHYROIDS

Ogawa,⁷ in 1925, reported that feeding parathyroid gland material to rats having fractures of the femur resulted in a callus of greater weight, greater ash and greater calcium content than that of the controls. French,¹⁴ in 1927, reported two clinical cases of fracture in old people (85 and 87 years of age) to whom parathyroid gland substance was administered by mouth. He felt that repair of the fracture in both

7. Ogawa, S.: *Arch. f. Exper. Path. u. Pharmacol.* **109**:83, 1925.

8. Dieterich, H.: *Arch. f. klin. Chir.* **136**:388, 1925.

9. Hammett, F. S.: *J. Biol. Chem.* **72**:527, 1927.

10. Chandler, S. B.: *Anat. Rec.* **35**:7, 1927.

11. Ravdin, I. S., and Morrison, M. E.: *Ossification After Fracture; Experimental Study*, *Arch. Surg.* **17**:813 (Nov.) 1928.

12. Ross, D. E.: *Relation of Parathyroids to Healing of Fracture as Controlled by Roentgen Rays*, *Arch. Surg.* **16**:922 (April) 1928.

13. Speed, K., and Rider, D. L.: *Experimental Healing of Bone After Parathyroidectomy*, *Arch. Surg.* **21**:679 (Oct.) 1930.

14. French, G. H.: *Endocrinology* **2**:25, 1927.

instances was facilitated by the treatment. Lehman and Cole,¹⁵ in 1927, reported experiments with parathormone administration in which they fractured the humerus in rats. Utilizing the ratio between the breaking strength of the healing humerus and that of the normal humerus as the criterion of repair, they found a slight difference in favor of the controls, and concluded that if the injection of parathyroid extract has any influence on the rate of calcification of fracture callus, it tends to delay the process. Hueper,¹⁶ in 1927, reported experiments in which he fractured the radius and ulna in cats, treating some with parathyroid extract. He reported a stimulation of the production and calcification of osteoid tissue and believed that parathyroid extract may be found to be of therapeutic value in cases in which the calcification and production of osteoid tissue is delayed, as, for instance, in the nonunion of fractures. Glässner and Hass,¹⁷ in 1928, reported experiments on the healing of fractures in cats with facilitation of callus formation and union on the administration of parathyroid extract. Ravdin and Morrison,¹¹ in 1928, reported that the administration of parathyroid extract to two dogs having fractures of the radius delayed the ossification in one, and concluded that parathyroid extract should be used with caution in cases of fracture. Fine and Brown,¹⁸ in 1928, reported experiments on dogs in which a defect was made in the femur with a trephine and in which subperiosteal rib resections were performed and the animals given parathyroid extract. They stated:

Although the number of experiments is small, it is reasonable to conclude that parathormone seems to delay the speed of deposition of calcium in regenerating bone of young dogs, whereas no clear evidence as to its potency in this or the reverse direction is available for adult dogs. The practical significance of these observations is that the clinical use of the extracts for delayed union is not based on any sound principle, can do little, if any good, and, in fact, may do harm.

Compere,¹⁹ in his review of the published reports of clinical cases of hyperparathyroidism, mentioned three cases in which fractures were present and tended to heal very slowly.

It is apparent from this incomplete review of the literature that with some exceptions most workers agree that following parathyroidectomy, or with varying degrees of parathyroid hypofunction, there is a deficiency or delay or both in the calcification and ossification of the callus of repair. There is considerably less agreement as to the influence of parathyroid hyperfunction or the administration of parathyroid preparations. It would be conceivably possible to harmonize or at least to

15. Lehman, E. P., and Cole, W. H.: Parathyroid Hormone and Calcification of Fracture Callus, *J. A. M. A.* **89**:587 (Aug. 20) 1927.

16. Hueper, W.: *Arch. Path. & Lab. Med.* **3**:1002, 1927.

17. Glässner, K., and Hass, J.: *Klin. Wchnschr.* **91**:1415, 1928.

18. Fine, J., and Brown, S.: *New England J. Med.* **198**:932, 1928.

19. Compere, E. L.: *Surg., Gynec. & Obst.* **50**:783, 1930.

interpret these discrepancies by a critical analysis of the various reports as to kind and number of animals used, dosage and route of administration of the parathyroid preparations used, criteria used in interpreting results, etc. We believe, however, that further data should be obtained before such an analysis would be profitable. The present experiments were performed in an effort to define more clearly the rôle of the parathyroids in the processes of ossification. We felt that the question as to why defective healing occurred after parathyroidectomy was still unanswered. Is the presence of the parathyroid hormone in the body necessary for the local processes of calcification and ossification? It is clear that the interpretation of the effects of parathyroid hyperfunction would largely depend on the answer to this question.

METHODS OF STUDY

We experimented with a number of methods in the search for one that would give comparatively uniform results in estimating the rate and degree of bone repair. At first we tried fractures of the femur. This we soon abandoned, as we found it difficult to maintain comparable immobilization in the various animals, and the times at which weight-bearing was permitted or complete healing occurred were extremely variable. We are quite in agreement with the opinion of many surgeons, as expressed by Henderson,²⁰ that local causes are far more often significant in the causation of delayed union than general or systemic causes, and that, therefore, in order to obtain any reliable information as to the influence of systemic changes, there must be no question of local factors interfering in the interpretation of results. In order to control the local factor of immobilization better, we next tried fractures of the tibia, produced by sawing across the shaft at the junction of the upper and middle third. This we tried in twenty dogs. Healing occurred, as well as we could judge, in 41, 42, 42, 44, 50, 50, 57, 65, 65, 70, 71, 72, 73, 75, 75, 75, 75, 80, 80 and 90 days, respectively. This lack of uniformity in a rather large series of controls left little basis on which to estimate the effect of systemic factors on the rate of repair. We next tried the method used by Haas²¹ in his experiments on the survival of bone after removal from the body. A metatarsal was aseptically removed from the foot, fractured in its middle portion, transplanted into the longitudinal muscles of the back, and then removed after approximately thirty days. This was done in twenty-four dogs, and while we were able to corroborate Haas' finding that some repair of the fracture takes place, the variability in degree was so great that this method was not suited to our purpose. The fourth method that was tried and subsequently employed was that of excising a segment from 2 to 3 cm. long from the anterior surface of the femur in its middle portion. Two cuts were made with a saw, approximately 40 per cent through the shaft of the femur, and the intervening segment was removed with a chisel. The periosteum of the segment was removed with it. This method had a number of advantages. The femur is readily accessible from a lateral incision, no muscles are cut across in exposing it, and the operation can be performed easily and quickly. It is convenient to take roentgenograms showing such a defect, and by means of roentgenograms follow

20. Henderson, M. S.: Ununited Fractures, *J. A. M. A.* **86**:81 (Jan. 9) 1926.

21. Haas, S. L.: Survival of Bone After Removal from the Body, *Arch. Surg.* **10**:196 (Jan.) 1925.

the repair that occurs. This method controls certain important local factors, in that there is no question of immobilization or interposition of soft parts, weight-bearing and use are not interfered with, and repair is thus constant in all the animals. A total of 110 such operations on dogs was performed. In eight animals the weakened femur subsequently fractured, and in one a local infection developed. Roentgenograms were taken at approximately ten day intervals, and the degree of repair was estimated independently by us and by two other workers in the laboratory. The average estimation of degree of repair expressed in terms of per cent of complete healing was then computed. In this way, it was possible to draw a curve expressing the rate of repair for any animal or series of animals.

RESULTS

Twenty control animals were operated on, and the rate of repair of the defect of the femur was observed. There was some variation in rate of the repair, but on the whole it was strikingly uniform. Distemper or diarrhea developed in five of the dogs during the course of the experimental period, and a noticeable reduction in the average rate of repair was shown when compared with that in those remaining in good health throughout. This seems to us to be an important factor and one that has not always received sufficient consideration in determining the effects of various factors on bone repair. It may be recalled in this connection that Thompson and Swarts²² reported their inability to determine the effect of parathyroidectomy on the healing of fractures in dogs because the cachexia and the poor condition of the parathyroidectomized dogs made comparison with normal controls impossible. Figure 1 shows a typical series of roentgenograms, and the estimated rates of healing are indicated by the curve in figure 4.

Thyroparathyroidectomy was performed on twenty-two dogs, in all of which a defect in the femur was produced. Tetany was controlled by the daily administration of from 20 to 30 Gm. of calcium lactate by mouth, with the occasional intravenous injection of 1 Gm. of calcium gluconate if severe tetany occurred. In spite of rather constant watchfulness, thirteen dogs did not complete the sixty day period considered desirable for observation, three fracturing the femur, three dying of distemper and seven dying of tetany. One dog showed no tetany or low blood calcium levels, and one was given parathormone. Seven dogs in which tetany had appeared completed the sixty day period, continuing in comparatively good health throughout. Specimen roentgenograms are shown in figure 2, and the curve representing the average rate of repair of the femur defect is shown in figure 4. Several features of this repair may be noted. The onset of repair was very much delayed, so that at the end of twenty days the estimated repair in the thyropa-

22. Thompson, R. L., and Swarts, J. L.: The Influence of the Thyroid and Parathyroid Glands on the Healing of Fractures, *J. A. M. A.* 57:724 (Aug. 26) 1911.

thyroidectomized dogs was less than half that of the control series. From this time on there was an improvement in the rate of repair, so that at the end of the sixty day period the average estimated repair was 65 per cent compared with 78 per cent for the controls. It may be noted here that tetany was rather frequent during the first three week period and comparatively infrequent during the remainder of the time. The possible significance of this will be discussed later.

In the dog in the series just described that showed no tetany or low blood calcium levels at any time following thyroparathyroidectomy, pronounced myxedema developed and a basal metabolic rate approximately 30 per cent below that calculated for the normal. It was felt that this case was therefore one of thyroid deficiency not complicated by parathyroid deficiency. The healing rate of the defect of the femur in this dog was parallel to that of the controls throughout. In another dog, following thyroparathyroidectomy, parathormone was administered daily in amounts sufficient to maintain the blood calcium at approximately normal levels. The healing rate of the defect of the femur in this dog was likewise parallel to that of the controls. These observations, confirmatory of those of Thompson and Swarts,²² led us to conclude that the thyroid deficiency necessarily accompanying the parathyroid deficiency when thyroparathyroidectomy is performed in the dog is not of material effect in the repair of a bone defect such as that produced.

Parathormone²³ was administered daily to twenty-two dogs in which a defect in the femur was produced. It was given subcutaneously in amounts of from $\frac{1}{2}$ to $2\frac{1}{2}$ units per kilogram of body weight. Four dogs receiving $2\frac{1}{2}$ units per kilogram per day died in from six to ten days with symptoms of parathormone overdosage, bloody diarrhea, etc. One dog receiving 2 units per kilogram died in ten days, one in nineteen days and one in sixty days. Three dogs receiving $1\frac{1}{2}$ units per kilogram lived through the experimental period of sixty days, as did six receiving 1 unit, and five receiving $\frac{1}{2}$ unit per kilogram of weight. In the fourteen dogs receiving from $\frac{1}{2}$ to $1\frac{1}{2}$ units of parathormone per kilogram per day and remaining in comparatively good health, the rate of healing of the femur defect was essentially the same as in the control series. In several of these dogs, there was evidence of abnormally situated and increased deposition of calcium in the callus very soon after the operation, which led us to expect facilitated repair, which did not subsequently materialize. In two dogs receiving parathormone the healing of the defect was definitely delayed, but these animals both showed anorexia, vomiting and bloody diarrhea of varying degree at different times, factors which in themselves might tend

23. Eli Lilly & Company furnished the parathormone used in these experiments.

to have this effect. We observed no delay or interference with the calcification of the callus in any of the animals that remained in good health during the period of administration of parathormone. In the case of four dogs, 20 Gm. of calcium lactate was given daily by mouth simultaneously with the administration of parathormone. The bone repair in these animals seemed to be slightly better than the average for the

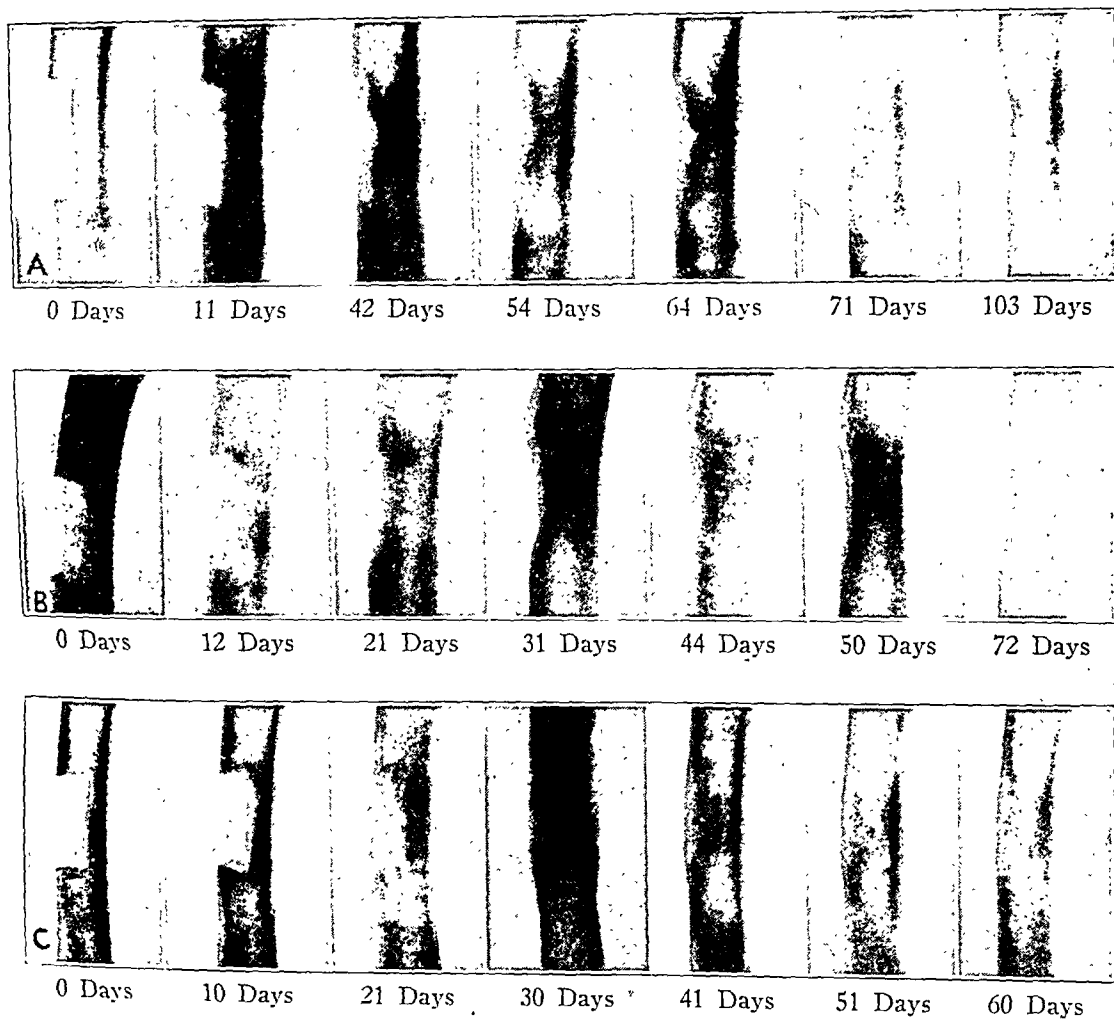


Fig. 1.—Roentgenograms showing repair of defects in the femurs of control dogs. Series *A* shows the right femur of dog B 15, *B* the left femur of dog B 25 and *C* the left femur of dog B 31 at stated intervals.

controls. We do not know the significance of this, and it may be that the use of a larger series of animals would make the difference disappear. Specimen roentgenograms are shown in figure 3 and the average curve of healing in figure 4.

COMMENT

Our experiments on thyroparathyroidectomized dogs showed definite delay in the healing of a bone defect when compared to that in the controls, confirming the reports of many investigators in this respect.

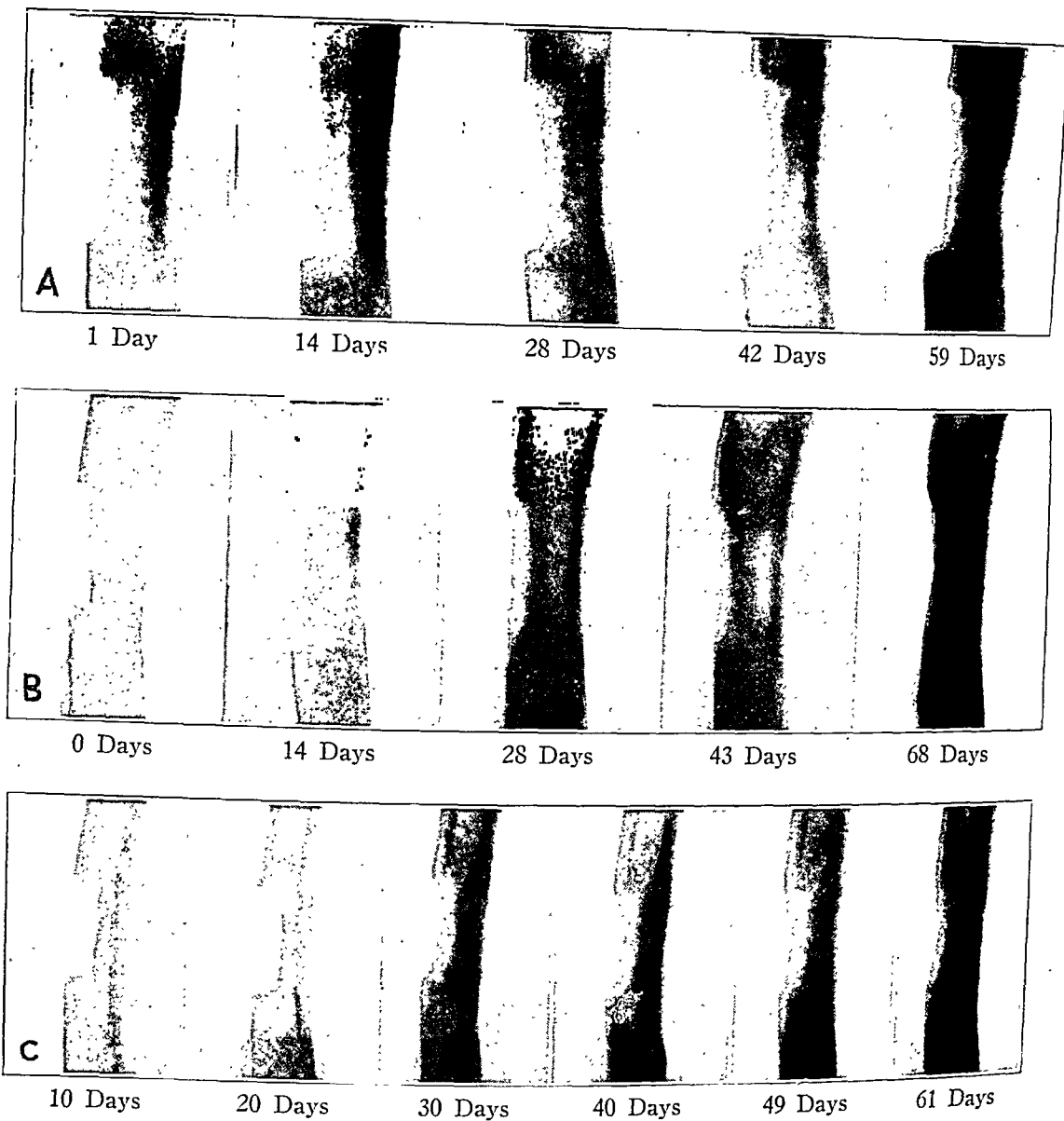


Fig. 2.—Roentgenograms showing the repair of defects in the femurs of thyroparathyroidectomized dog. Series *A* shows the right femur of dog A 11, *B* the right femur of dog A 16 and *C* the left femur of dog B 35 at stated intervals.

In the beginning of these experiments, we cherished the notion or hope that it could be shown that one function of the parathyroids was concerned with the local or actual process of ossification. As the experiments progressed, however, we were more and more impressed by the

fact that healing and repair did occur with the complete absence of these glands, and were correspondingly less impressed with the observation that this repair was delayed. The most marked period of the delayed repair in the case of parathyroidectomized dogs was in the first two to three weeks. During this period, tetany was as a rule only incompletely controlled, occurring practically every day, and thus in a non-

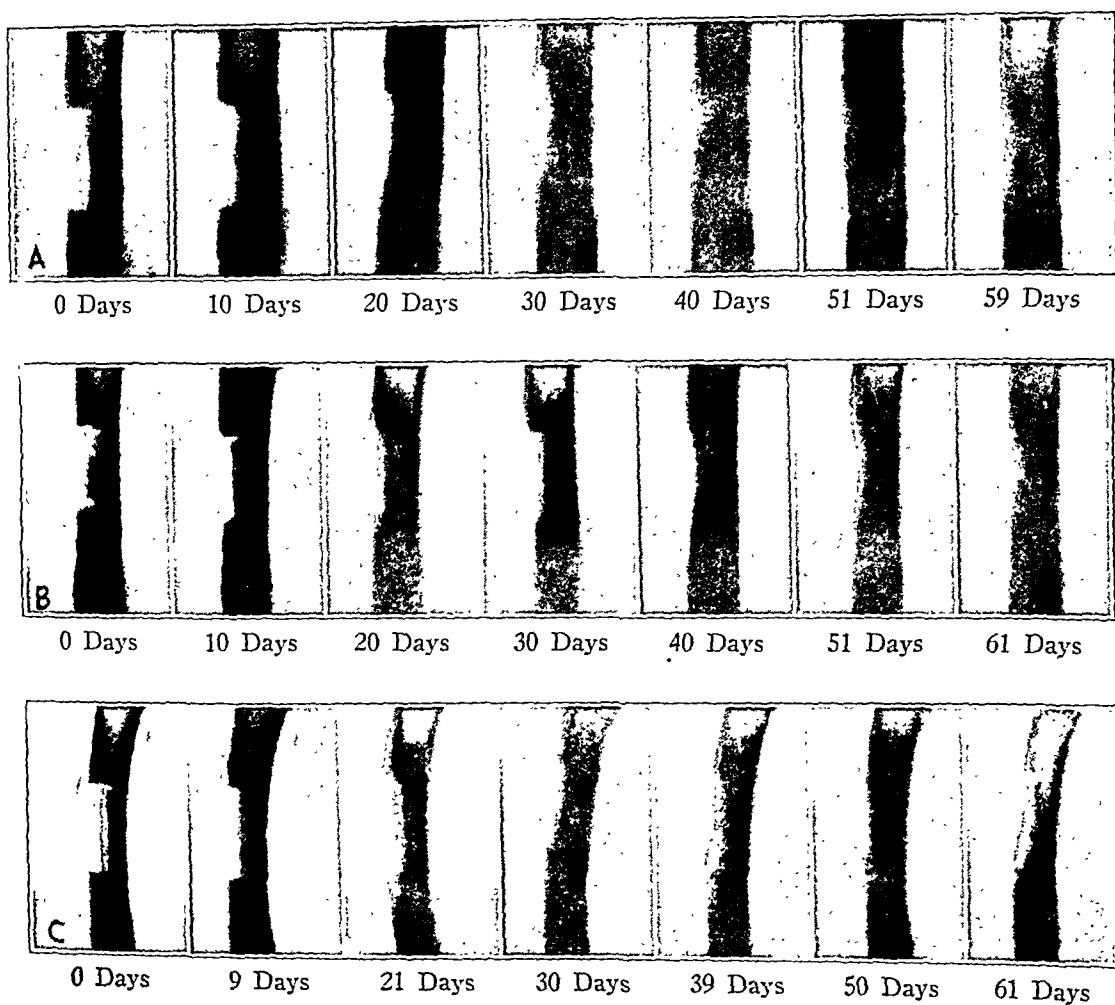


Fig. 3.—Roentgenograms showing the repair of defects in the femurs of dogs given parathormone. Series *A* shows the left femur of dog B9, *B* the left femur of dog B16 and *C* the left femur of dog B13 at stated intervals.

specific way interfering with the feeding and rest of the animal. As the tetany became more completely controlled, the rate of repair began to approximate that of the controls. With intermittent administration of calcium (given once or at most twice daily), the restoration of the blood calcium level toward normal values was correspondingly intermittent. A detailed analysis of this was made in several instances.

Thus in one dog shortly after thyroparathyroidectomy the tabulated data were obtained.

It is thus seen that during the first two weeks or so following the thyroparathyroidectomy, the blood calcium approached normal levels for only a short part of the time, while after from two to three weeks, the same type of single daily administration of calcium kept the blood calcium values approximately normal for the greater part of the time. It seems significant that the gradual improvement in the process of repair corresponds with this more adequate maintenance of the blood calcium level. It seems necessary to conclude, therefore, that the local processes of calcification and ossification occurring in a region of repair do not require the parathyroid hormone itself, and that if changes in

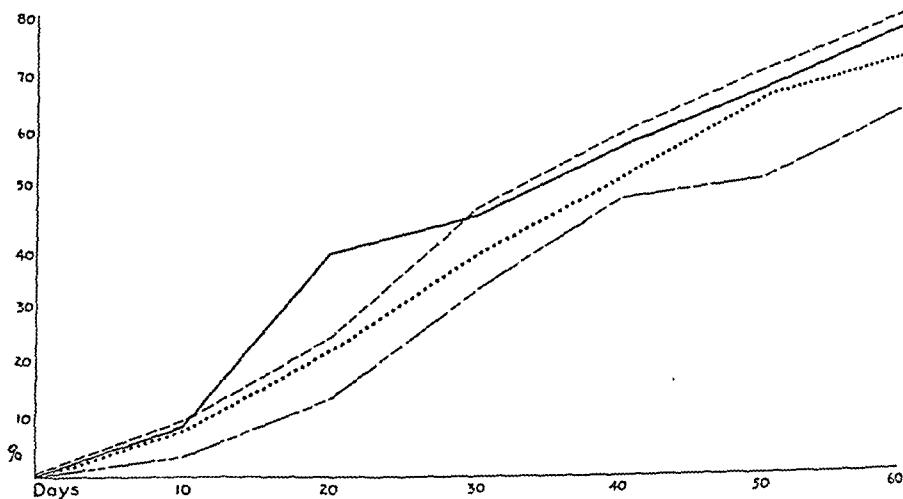


Fig. 4.—Chart showing the healing rate of femur defects in dogs. The average rate of fifteen normal controls is shown by ———; the average rate of twelve dogs given parathormone by — — — —; the average rate of four sickly controls by ······, and the average rate of seven thyroparathyroidectomized dogs by — · — · —.

the chemical composition of the blood following parathyroidectomy can be prevented or compensated for, normal repair would result. Histologic examination after repair had progressed nearly to completion gave no evidence of abnormality in the repair. Chemical examinations were not made. Shelling²⁴ recently reported that the calcification of the repair callus in rats after fracture and parathyroidectomy is markedly affected by the diet, and that the addition of calcium increases the density of the callus.

With this conception of the rôle of the parathyroids in the process of calcification and ossification, we can approach the discussion of the

24. Shelling, D. H.: *Proc. Soc. Exper. Biol. & Med.* 28:306, 1930.

possible influence of parathyroid hyperfunction as produced by the administration of parathormone. Parathyroidectomy results in a diminished process of bone repair. Administration of parathyroid hormone in adequate dosage to parathyroidectomized dogs restores the repair process to normal. On the basis of these observations, if the parathyroid hormone either acted as a stimulant to the local process of repair or took part directly in this process, it would appear logical to expect that the administration of parathyroid hormone to a normal dog would facilitate or increase the repair process. As, however, the evidence indicates that the diminished repair resulting from parathyroidectomy is related to the altered chemical state of the blood caused by the parathyroid deficiency and not to the parathyroid deficiency *per se*, and can be compensated for by adequate administration of calcium, we cannot assume any bone stimulant function on the part of the para-

Blood Calcium Level in a Dog After the Administration of Calcium Lactate

		Blood Calcium per 100 Cc.
8:00 a. m.	Tetany.....	4.4
8:30 a. m.	30 Gm. of calcium lactate by mouth	
10:00 a. m.	No tetany.....	7.2
12:00 m.	No tetany.....	9.9
2:00 p. m.	No tetany.....	9.4
4:00 p. m.	No tetany.....	9.5
8:00 p. m.	No tetany.....	8.8
8:00 a. m.	Tetany.....	6.0
Two Weeks Later		
8:00 a. m.	Some rigidity.....	8.5
8:30 a. m.	30 Gm. of calcium lactate	
10:00 a. m.	10.1
12:00 m.	11.9
2:00 p. m.	14.7
4:00 p. m.	11.0
8:00 p. m.	10.5
8:00 a. m.	9.0

thyroids. The inability to demonstrate any augmentation of the repair process by the administration of parathormone is evidence of this. It might also indicate that the normal chemical composition of the blood is optimal for the repair process, and that the latter cannot be benefited by supernormal levels of blood calcium. There is considerable clinical as well as experimental evidence that the raised level of blood calcium in hyperparathyroidism is due to a withdrawal of calcium from the bones. This decalcifying process would appear to be directly opposed to the normal process of calcification occurring in the repair of a fracture or a bone defect. The clinical evidence appears to support this view. The impaired healing seen in a number of the dogs receiving parathormone would be in harmony with these reports. As these dogs frequently showed anorexia, vomiting and bloody diarrhea, it is difficult to distinguish clearly the effects directly attributable to such a decalcifying process from those due to the marked disturbance in diges-

tion. It is probable that an artificial hyperparathyroidism without gastro-intestinal disturbance might be produced by a more appropriate administration of parathormone than that used in these experiments. It should be noted here that Allison and Brooks²⁵ have reported that atrophy of the bone from disuse did not materially affect the process of bone regeneration, and they concluded that a region of regeneration or repair is seemingly able to commandeer its requisite salts even though adjacent bone is gradually being decalcified.

CONCLUSIONS

1. The rate of repair of a defect in the dog's femur is reasonably consistent throughout a series of animals if all are healthy and show a good appetite during the experimental period. Dogs that are sickly from distemper, diarrhea or other causes show a definite though not great impairment of the rate of bone repair. This fact should be taken into consideration in all experimental work on growth of bone or repair after injury or fracture.

2. Thyroparathyroidectomy in the dog definitely delays the healing of a bone defect. Healing goes on to completion, however, and is less delayed and approximates the normal if the administration of calcium is such as to maintain the blood calcium level nearly normal. The presence of the parathyroid hormone itself does not seem to be necessary for the process of calcification and ossification.

3. The effect of parathormone on the repair of a bone defect is somewhat complicated. In several dogs the administration of parathormone was followed by the very early appearance of calcium deposition in the callus as judged by roentgenograms, conveying the impression of a facilitated repair. The time of complete healing, however, was not changed. When parathormone was given in reasonably large amounts throughout the experimental period, a definite impairment of healing could be seen. Such dogs, however, frequently exhibited bloody diarrhea and loss of appetite, effects that complicate the interpretation. It does not appear probable that the administration of parathormone will facilitate bone repair in any case except one of parathyroid deficiency.

4. Thyroid deficiency uncomplicated by parathyroid deficiency did not delay the healing of a bone defect.

25. Allison, N., and Brooks, B.: Bone Atrophy, *Arch. Surg.* 5:499 (Nov.) 1922.

TENNIS ELBOW (EPICONDYLITIS) CAUSED BY RADIOHUMERAL BURSITIS

ANATOMIC, CLINICAL, ROENTGENOLOGIC AND PATHOLOGIC ASPECTS,
WITH A SUGGESTION AS TO TREATMENT

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THE CLINICAL SYNDROME

The term "tennis elbow" (epicondylitis, epicondylalgia) is a misnomer. The condition occurs in adults as a result not only of sports requiring the use of a racket (tennis, squash, court tennis) but of others, such as golf and baseball, and of occupations demanding lifting and sudden flexion and extension of the elbow, such as are required of pressers of clothing, salesmen carrying grips, violinists, blacksmiths, telephone operators and housewives. Direct trauma over the lateral aspect of the elbow may also cause this condition. Tennis elbow is frequently diagnosed as sprain or rheumatism, and the name is applied to a clinical syndrome of varying intensity characterized by pain and tenderness and sometimes accompanied by swelling and heat in the region of the epicondyle. The pain may be of a sudden, sharp, darting character causing a quick cessation of the movement involved in its production, or it may be dull and constant, with radiation to the arm or forearm and hand. Extension at the elbow, pronation, supination and tight flexion of the fingers often increase the pain, while extension at the wrist sometimes relieves it. Weakness of the extensor muscles of the forearm is usually present, with an accompanying weak hand grip and difficulty in lifting. Patients afflicted in a severe degree with this condition are exceedingly helpless, and become impatient because of the symptomatic remissions that may occur over weeks, months or years. The entire condition is characterized by symptoms and signs that are far more marked than the pathologic anatomy would seem to indicate.

HISTORICAL REVIEW

Bernhardt,¹ in 1896, is credited with the first description of the condition; he thought it was neuralgia. There were other contribu-

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1. Bernhardt, M.: Ueber eine wenig bekannte Form der Beschaeftigungsneuralgie. *Neurol. Zentralbl.* **15**:13, 1896.

tions up to about 1910, when the subject received consideration by a number of German writers (Vulliet,² Franke,³ Momburg,⁴ Bernhardt⁵) who attributed the cause to neuralgia, periostitis, involvement of the capsule of the elbow joint or a strain. Further studies were made by Coues,⁶ in 1914, and Dubs⁷ in 1920, both of whom reviewed the literature, and by Carp⁸ in 1921. In 1921 Schmitt⁹ reported a case of calcified radiohumeral bursitis in which he performed an operation. In 1922, Osgood¹⁰ also described the radiohumeral bursa and the clinical picture resulting from its inflammation. This coincided in most respects with previous descriptions of epicondylitis and tennis elbow. He stressed the occurrence of a small swelling just beneath the epicondyle over the radiohumeral joint, which may be noted by careful observation and comparison with the other side. He described some conservative therapeutic measures, and in obstinate cases recommended exploration over the radiohumeral joint and excision of the bursa, if inflammation was present. Since then other authors have advanced various theories concerning the etiology of tennis elbow and have recommended different methods of treatment. The causes suggested, in brief, are as follows:

1. Periostitis of the epicondyle (The epicondyle has no periosteum, so that the condition is really an osteitis.) (Bergman,¹¹ Bertocchi,¹² Ferraro,¹³ Merlini,¹⁴ Frey¹⁵)

2. Vulliet, H.: Die Epicondylitis humeri, *Zentralbl. f. Chir.* **37**:1311, 1910.

3. Franke, Felix: Ueber Epicondylitis humeri, *Deutsche med. Wchnschr.* **36**:13 and 420, 1910.

4. Momburg: Ueber Periostitis am Epicondylus humeri, *Deutsche med. Wchnschr.* **36**:260 (Feb. 10) 1910.

5. Bernhardt: Bemerkungen zu dem Aufsatz, cited by Franke: Ueber Epicondylitis humeri, *Deutsche med. Wchnschr.* **36**:221 (Feb. 3) 1910.

6. Coues, William Pearce: Epicondylitis (Franke) or Tennis Elbow, Boston M. & S. J. **170**:461 (March 26) 1914.

7. Dubs, J.: Zur Frage der sogenannten Epicondylitis humeri (Vulliet-Franke), *Schweiz. med. Wchnschr.* **1**:166 (Feb. 26) and 187 (March 4) 1920.

8. Carp, Louis: Epicondylitis humeri, *Surg., Gynec. & Obst.* **33**:257 (March) 1921.

9. Schmitt, Josef: Bursitis calcarea am Epicondylus externus humeri. Ein Beitrag zur Pathogenese der Epicondylitis, *Arch. f. Orthop.* **19**:215, 1921.

10. Osgood, Robert B.: Radiohumeral Bursitis, Epicondylitis, Epicondylalgia (Tennis Elbow), *Arch. Surg.* **4**:420 (March) 1922.

11. Bergmann, Ernst: Epikondylitis, *Arch. f. Orthop.* **23**:368, 1925.

12. Bertocchi, Andrea: Contributo allo studio dell' epicondilitite omerale, *Ann. ital. di chir.* **5**:332 (April 30) 1926.

13. Ferrero, V.: L'epicondilitite dell' omero, *Arch. di ortop.* **44**:740, 1928.

14. Merlini, Antonio: L'epicondilitite omerale, *Arch. di ortop.* **44**:546, 1928.

15. Frey, Egan: Zur Behandlung der Epikondylitis, *Wien. med. Wchnschr.* **78**:764 (June 9) 1928.

2. Myofascitis of the extensor origins (Cooke,¹⁶ Romer,¹⁷ Edgar,¹⁸ Cluzet,¹⁹ Bryce,²⁰ Hansson and Horwich²¹)
3. Radiohumeral bursitis (Schueller,²² Carter,²³ Dittrich²⁴)
4. Arthritis of the radiohumeral joint (Wachendorf,²⁵ Ochsenius²⁶)
5. Tear in the muscular portion of the extensor carpi radialis longus (Rosenburg²⁷)
6. Involvement of the capsule of the elbow joint (Glass²⁸)
7. Involvement of the subcutaneous fat and fascia and the periosteum of epicondyle (Fischer²⁹)
8. Malalignment of the radial head and of the lower end of the humerus (Brandesky³⁰)
9. Adhesions (Mills³¹)
10. Fixation of the radial head in the normal range of motion (Marlin³²)

The types of therapy that have been proposed are:

1. Rest (advised by all authors)
2. Physical therapy (Cooke,¹⁶ Romer,¹⁷ Edgar,¹⁸ Bergmann,¹¹ Rosenburg,²⁷ Carter,²³ Bertocchi,¹² Glass,²⁸ Frey,¹³ Ferrero¹³)

16. Cooke, L.: Tennis Elbow, *Indian M. Gaz.* **57**:130, 1922.

17. Romer, Frank: Some Observations on "Tennis Elbow," *Lancet* **2**:67 (July 8) 1922.

18. Edgar, W. H.: Tennis Elbow, *J. Roy. Nav. M. Serv.* **9**:1922, 1923.

19. Cluzet, J.: Sur l'épicondylite et son traitement par les agents physiques, *Arch. d'électric. méd.* **34**:190 (May) 1926.

20. Bryce, Alexander: A Case of "Tennis Elbow" Treated by Luminous Heat, *Brit. J. Actinotherapy* **5**:55 (June) 1930.

21. Hansson, K. G., and Horwich, I. D.: Epicondylitis Humeri, *J. A. M. A.* **96**:1557 (May 17) 1930.

22. Schueller, M. P.: Epicondylitis tuberculosa, *Med. Klin.* **19**:1227 (Sept. 13) 1923.

23. Carter, Ralph M.: Epicondylitis, *J. Bone & Joint Surg.* **23**:553, 1925.

24. Dittrich, R. J.: Radiohumeral Bursitis (Tennis Elbow); Report of Two Cases, *Am. J. Surg.* **7**:411 (Sept.) 1929.

25. Wachendorf, Kurt: Epicondylitis humeri, ein Beitrag zur Entstehung und Lokalisation dieser Erkrankung, *Deutsche med. Wchnschr.* **50**:1215 (Sept. 5) 1924.

26. Ochsenius, Kurt: Ueber die Prognose des Tennisellbogens, *Deutsche med. Wchnschr.* **51**:1988 (Nov. 27) 1925.

27. Rosenburg, Gustav: Tennisellenbogen und Muskelriss, *Med. Klin.* **21**:779 (May 27) 1925.

28. Glass, E.: Beitrag zur sogenannten "Epicondylitis humeri" (Sportverletzung, Selbstbeobachtung), *Zentralbl. f. Chir.* **56**:724 (March 23) 1929.

29. Fischer, A. W.: Ueber die Epicondylus und Styloides—Neuralgie, ihre Pathogenese und zweckmaessige Therapie, *Arch. f. klin. Chir.* **125**:749, 1923.

30. Brandesky, Walter: Ueber den Epicondylusschmerz, *Deutsche Ztschr. f. Chir.* **219**:246 (Aug.) 1929.

31. Mills, C. P.: The Treatment of "Tennis Elbow," *Brit. M. J.* **1**:12 (Jan. 7) 1928.

32. Marlin, Thomas: Treatment of "Tennis Elbow" with some Observations on Joint Manipulation, *Lancet* **1**:509 (March 8) 1930.

3. Manipulation (Mills³¹ advised sudden extension of the forearm while it is in pronation and while the fingers are flexed with the patient under a general anesthetic. At the same time he put pressure over the epicondyle. He heard a snap and thought that adhesions were broken. Sudden extension of the forearm was also advised by Marlin³² and Bryce²⁰)

4. Excision of the radiohumeral bursa (Schueller,²² Carter,²³ Dittrich,²⁴ Kleinberg³³)

5. Methods to relax the extensors:

(a) Strapping the forearm (Cooke,¹⁶ Romer,¹⁷ Marlin³²)

(b) Cock-up splint (Hansson and Horwich²¹)

6. Roentgen therapy (Guetig,³⁴ Cluzet,¹⁰ Merlini¹⁴)

7. Excision of the subcutaneous fat and fascia and the periosteum of the epicondyle (Fischer²⁹)

8. Infiltration of the tender tissues with procaine hydrochloride in saline solution (Sandrock³⁵)

This study is based on the following considerations: It is difficult to ascribe an individual case of tennis elbow to any particular cause, unless this cause is proved. Generally speaking, an involved conjoined tendon at the epicondyle or its movement or strain in the presence of an inflamed structure or structures in close proximity may produce tennis elbow in varying degrees. These structures are: (1) the radiohumeral bursa; (2) the epicondyle; (3) the conjoined tendon at the epicondyle; (4) the capsule of the elbow joint; (5) the radiohumeral joint, and (6) the radial nerve.

RADIOHUMERAL BURSITIS

Anatomy.—It is established that a radiohumeral bursa exists, probably adventitiously. I have seen it on the dissecting table (fig. 1). Gruber³⁶ found it in one out of six cadavers, Osgood¹⁰ dissected it out, and Grinnell,³⁷ in routine dissections of the elbow in eighteen cadavers, nearly all males, found nine bursae on the right side and six on the left. Five of these were bilateral. The bursa is also mentioned by Vogt,³⁸ Broesike,³⁹ Bardenheuer⁴⁰ and Heineke.⁴¹ It is difficult to

33. Kleinberg, Samuel: See report of case 5.

34. Guetig, Carl: Beitrag zur Behandlung der Epikondylitis, *Med. Klin.* **19**:535 (April 26) 1923.

35. Sandrock: Epicondylitis Humeri, Periostitis et Styloiditis radii sinistra, *Zentralbl. f. Chir.* **52**:1897 (Aug. 22) 1925.

36. Gruber, quoted by Schmitt (footnote 9).

37. Grinnell, Robert S.: Personal communication to the author.

38. Vogt, quoted by Schmitt (footnote 9).

39. Broesike, Gustav: Lehrbuch der normalen Anatomie des menschlichen Körpers, Berlin, Fischers medicinische Buchhandlung, H. Kornfeld, 1899.

40. Bardenheuer, Bernhard: Die Verletzungen der oberen Extremitäten, Stuttgart, Ferdinand Enke, 1886.

41. Heineke, quoted by Schmitt (footnote 9).

see in a routine dissection. It lies beneath the conjoined tendon, just below the epicondyle and over the radiohumeral joint. Normally it is about 1 by 0.5 cm. and its walls are very thin and friable. It may appear only as a slight depression or elevation, and when incised is usually found to contain a little clear fluid. Pathologically, its approximate position is demonstrated by the shadows due to calcification, as seen in figures 3A, 4, 8A and 9A, in which the bursae encroach on the epicondyle or extend over the head of the radius. Schmitt,⁹ Osgood,¹⁰

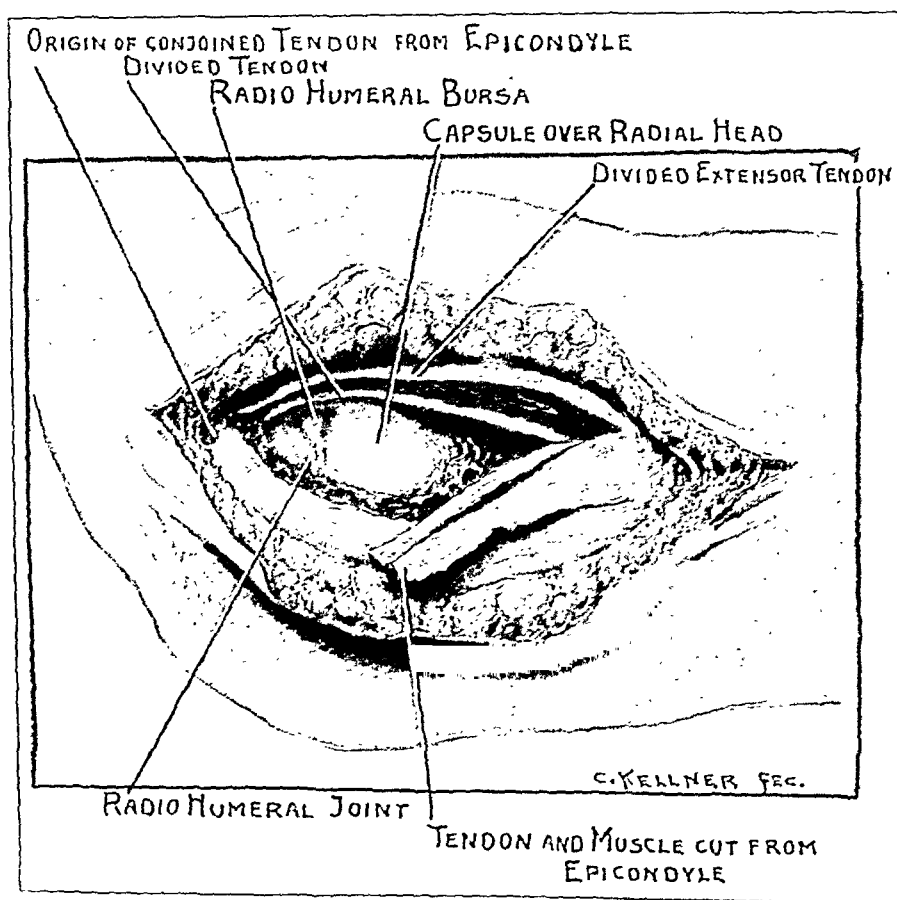


Fig. 1.—Drawing of a dissection, showing the radiohumeral bursa in relation to the surrounding structures.

Schueller,²² Dittrich²⁴ and Kleinberg²³ have seen the bursa in a pathologic condition on the operating table.

Treatment.—Clinical, roentgenologic, conservative therapeutic, operative and pathologic evidence will be advanced to show that involvement of the radiohumeral bursa may produce tennis elbow. The conservative treatment in four of the eight cases reported consisted in firm digital pressure over the bursa in order to rupture it. The immediate alleviation of symptoms and almost complete disappearance of signs were dramatic.

REPORT OF CASES⁴²

CASE 1.—*Tennis elbow caused by calcified radiohumeral bursitis, the result of direct trauma. Positive roentgenographic findings. Rupture of bursa by digital pressure. Prompt relief with almost complete disappearance of shadow in the roentgenogram.*

An American housewife, aged 25, was admitted to the outpatient department of the Presbyterian Hospital on Feb. 27, 1928. She worked as a cutter and used medium-sized scissors with her left hand. In this act she frequently struck the outer side of her elbow against the edge of the table. While she was working, eleven hours before admission, she had a sudden onset of increasing pain, swelling (fig. 2) and tenderness on the outer side of the left elbow. The pain was "beating" and was localized, except for occasional radiation down the dorsal radial region of the forearm. It was aggravated by any movement of the elbow, and was worse at night so that she could not sleep. Relief was obtained by hot wet applications. She had practically complete disability of the left elbow and hand.

The patient had had no cold or sore throat, nor was there a previous history of rheumatism.

Examination of the left elbow showed it to be flexed to a right angle and held guardedly. The patient was in pain. There was moderate swelling over the



Fig. 2.—Photograph of elbows in case 1, showing the swelling in the region of the left epicondyle caused by an involved radiohumeral bursa.

epicondyle so that the circumference of the elbow on this side was 2 cm. greater than that on the opposite side. There was exquisite tenderness, even to very light pressure, extending from the lateral aspect of the radiohumeral joint to the epicondyle, and there were moderate heat and slight redness. All movements at the elbow were so painful that an accurate range of motion could not be obtained. Sudden extension of the forearm, pronation and supination produced much pain at the elbow; this pain was also marked when the fingers were flexed with the wrist in volar flexion. The hand grip was extremely weak and picking up small objects was almost impossible.

The temperature was 99.6 F. The white blood cells numbered 13,000, with 67 per cent polymorphonuclears. The urine was acid; there was a faint trace of albumin but no dextrose. Microscopically it was observed to contain urates, mucus and a few granular casts and white blood cells. A few teeth showed caries. The throat was normal.

The roentgenogram (fig. 3 A) showed a segmented, oval shadow of the density of bone, 1.3 by 0.6 cm., just lateral to the epicondyle. There was an area of decreased density 2.5 by 1.4 cm. around the shadow.

42. There are now under observation three additional cases of calcified radiohumeral bursitis. The late results of therapy are not yet available.

The diagnosis was acute radiohumeral bursitis with calcification.

The therapy recommended was the use of a sling, baking and the administration of salicylates and codeine. The patient returned to the emergency ward the same evening because the elbow was so painful, even with medication, that she could not rest. She was given more codeine and amidopyrine, and local applications were made of solutions of lead and opium.

March 1: The temperature was 99.6 F. There was no improvement; the pain was even more severe, and the patient could not sleep. The tenderness persisted. The dorsal surface of the forearm was strapped to relieve the tension of the extensor muscle group. One-eighth grain of morphine (0.008 Gm.) was administered at 11:30 a. m.; the pain continued. Ten grains (0.65 Gm.) of

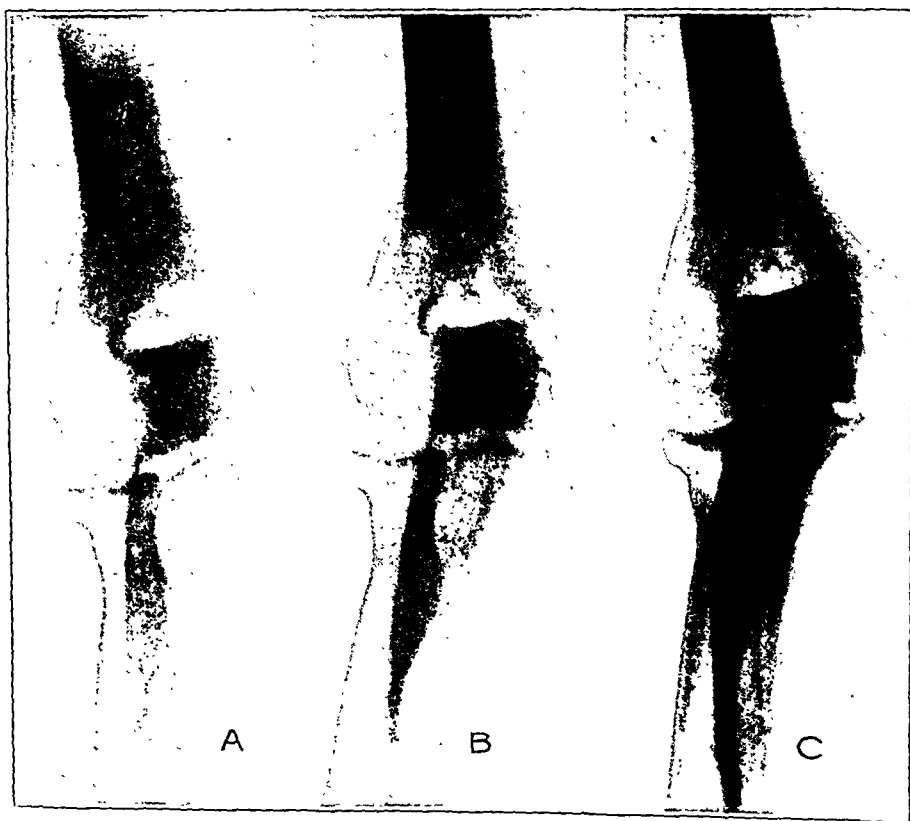


Fig. 3.—Roentgenograms of left elbow in case 1. *A* shows an irregular oval shadow just lateral to the epicondyle. This shadow represents a calcified radiohumeral bursa beneath the conjoined tendon. *B* was taken immediately after the bursa had been ruptured by digital pressure producing prompt relief. Note the dispersed and faint shadow just lateral to the epicondyle. *C*, taken three days later. Note the almost complete disappearance of the shadow seen in view *B*.

acetylsalicylic acid was given at 12:45; the pain was not relieved. Physical therapy (radiant light and static effluve) was used between 2 and 3 p. m.

March 2: The patient was definitely relieved and was able to sleep all night without medication. There was no pain when the elbow was quiet, and pain was slight on flexion and extension. These motions were limited. Swelling and heat were still present. The tenderness was less marked, and there was moderate edema of the skin over the bursa. The hand grip was much stronger. The strapping

was removed. The patient took 10 grains of acetylsalicylic acid at 11 a. m. and at 2, 6 and 10 p. m.

March 3: The elbow was more painful than on the previous day, but the patient slept during the night. She thought the strapping eased the pain. The swelling and tenderness were less, and there was more comfort when the forearm was placed in a sling. Flexion was almost complete, and extension was possible up to 150 degrees. Flexion of the fingers with the wrist in volar flexion was slightly painful around the elbow; with the wrist in extension there was no pain. The edema of the skin over the bursa was diminished. The patient was given physical therapy and the acetylsalicylic acid was stopped.

March 5: The pain was worse than two days previously, but not severe enough to inconvenience the patient. The swelling was still present, but was more localized. The tenderness was very slight, and in the course of deep palpation something was felt to crunch under the finger just as when a ganglion is broken with the fingers. The patient also felt this. The bursa had ruptured. A roentgenogram taken immediately (fig. 3 B) showed the shadow previously reported to be diminished in density and less distinct.

March 6: There was no pain, and all motions in the elbow were free except extension, which was limited to 170 degrees. There were very slight tenderness and swelling over the radiohumeral joint. All therapy was stopped.

March 7: The patient began to do all her factory work and housework without pain.

March 8: The roentgenogram did not show the shadow that was reported three days previously, but only a slight suggestion of dispersed density.

March 10: Slight swelling and tenderness over the lateral aspect of the elbow persisted. Extension and flexion of the elbow were complete. The hand grip was good.

March 24: The patient was working, and there were no symptoms or signs. The roentgenogram showed no evidence of the shadow reported on February 27.

The patient has disappeared from observation.

CASE 2.—Tennis elbow in a squash player. Prompt relief by firm digital pressure over the epicondyle and radiohumeral joint. Results observed for eighteen months.

H. H., an American merchant, aged 33, in excellent physical condition, consulted me on Sept. 6, 1929, because of pain in the right elbow of four months' duration. He began to play squash-tennis sixteen months prior to examination and continued to do so irregularly until about four months previously when he began to have pain in the right elbow on gripping the racket tightly as he tried to follow through on a backhand stroke. As the game progressed, the pain increased so that he always felt like stopping. Rest gave him relief, but the disabling pain recurred when he played again. He had a little pain on the outer side of his elbow, even when not playing. He noticed an increasing weakness of his right hand in the grasping movement, so that lifting a cup to his mouth, cutting food and the use of a toothbrush became extremely difficult. Sometimes this weakness was so marked that objects fell out of his hand. In pulling the ends to tie a bow tie he felt as though "a red hot poker was being stuck into his elbow." Touching or striking the outer aspect of the elbow produced tenderness.

Examination of the right elbow showed slight swelling over the radiohumeral joint and exquisite tenderness over this swelling. The grip of the right hand was extremely weak, and there was difficulty in picking up light objects because of this weakness and the pain in the elbow. Extension, pronation and supination were painful.

The patient was asked to lie down on the examining table, and firm digital pressure was applied over the tender and swollen area on the lateral aspect of the elbow for about two minutes. The procedure produced a great deal of pain, but he was willing to stand it. The immediate effects of the manipulation were dramatic: The pain and tenderness disappeared, the hand grip was firm, and the patient enthusiastically lifted one end of the examining table with the right hand without any trouble. He was instructed to play squash the same evening and did so without much trouble. Slight soreness persisted on the outer aspect of the elbow for about two weeks, but there was no real disability or pain. On several occasions he had difficulty in tightening a bow tie because of pain in the elbow and weakness of the hand. A roentgenogram of the elbow on Nov. 29, 1929, was negative.

The patient has been followed up for about eighteen months. There has been no recurrence of his symptoms. He plays in tournaments of squash-tennis repeatedly.

CASE 3.—Tennis elbow caused by direct and indirect trauma in a tennis and handball player. Quick relief by firm digital pressure over the epicondyle and radiohumeral joint. Results observed for nineteen months.

F. M., an American executive, aged 35, muscular and in excellent condition, consulted me on Aug. 6, 1929, because of pain in the right elbow and partial disability of the right hand. He had engaged in athletics for many years, participating especially in tennis and handball. Seven weeks previously he struck his right elbow against a block of iron while walking. He had momentary pain and thought nothing more of the incident. Two days later, while playing handball, he noticed that he "could not get his serve going." In order to produce his most forceful serve he was accustomed to snap his right wrist so that the hand was brought in supination. The service was poor, and with each stroke he had a twinge of pain on the outer side of his elbow. After the game he had a sensation of numbness in the right hand. He took some heat treatments, which improved the condition only temporarily. He could not play tennis because during the service he had severe pain in the right elbow. He continued to play handball poorly, but modified his game in such a way that the snap in his wrist was lacking. His right hand was so weak that he had difficulty in lifting and in fastening his tie. Most of his motions were accomplished by scapular movement, even the lifting of a cup to his mouth. There was no loss of sleep when he kept his arm in a guarded position.

Examination of the right elbow showed an exquisite point of tenderness over the radiohumeral joint. The hand grip was very weak and caused pain in the outer side of the elbow and forearm. There was difficulty in lifting, and the pain was increased by sudden extension of the forearm or supination. Dorsal flexion of the hand relieved the pain.

The patient was asked to lie down on the examining table, and firm digital pressure with the thumb was applied over the radiohumeral joint. This produced much tenderness and radiating pain down the forearm. Immediately after the procedure the hand grip was much stronger, and the numbness of the hand disappeared. The pain in the outer aspect of the elbow was less severe. Radiant heat and diathermy were then applied to the outer aspect of the elbow, and the forearm was strapped. The strength of the hand quickly became normal, and its numbness disappeared. Two and six days later, the symptoms and signs were practically gone, but the patient was given more physical therapy. Handball and tennis were not permitted for two weeks. He then began to play again, and has had no trouble up to the time of this report, a period of nineteen months. During this period he has been examined a number of times.

CASE 4.—*Tennis elbow caused by repeated lifting. Quick relief by firm digital pressure over the epicondyle and radiohumeral joint. Results observed for fourteen months.*

S. G., an American lawyer, aged 37, in good general condition, consulted me on March 30, 1930, because of transitory pain in the right elbow of two months' duration. As he expressed it, there seemed to be "too many bones" there. When he closed his hand tightly or attempted to lift even a light object, he had pain in the outer side of the elbow. There was no pain without motion. He ascribed the condition to the fact that he had repeatedly lifted with his right hand an electric sewing machine weighing about 35 pounds from the floor to a table. The previous summer he had played golf a good deal, but had no trouble at that time.

On examination of the right elbow, there was no detectable swelling over the radiohumeral joint, but the area was exquisitely tender. The grip of the right hand was weak, and the patient had difficulty in lifting with the forearm in complete extension, both in pronation and in supination. He had pain in the outer side of the elbow when the fingers were completely flexed with the wrist in extension or flexion.

The patient was asked to lie down on the examining table, and firm intermittent pressure with the thumbs was exerted over the radiohumeral joint. This procedure caused considerable pain. Immediately after the manipulation, there was very little tenderness over the radiohumeral joint. The hand grip was much stronger, lifting was easier, and there was only slight pain in the elbow when the fingers were flexed. He had practically no symptoms until two weeks later, when the pain, tenderness and weakness of the hand grip recurred, three days after appendectomy for acute gangrenous appendicitis. The symptoms in the elbow lasted for about forty-eight hours, and were relieved by rest of the forearm with the hand in extension and by the application of radiant heat to the radiohumeral joint.

The patient has been followed for fourteen months, and there has been no recurrence of any symptoms or signs referable to the right upper extremity.

CASE 5.—*Tennis elbow in a tinsmith, caused by calcified radiohumeral bursitis. Roentgenographic, operative and pathologic findings. Results observed for twelve months.*

M. H., a tinsmith, born in Russia, 52 years old, was admitted to the orthopedic service of Dr. Samuel Kleinberg at the Hospital for Joint Diseases on May 8, 1930, complaining of pain in the outer side of the right elbow of eight weeks' duration. The pain was present on motion of the elbow, especially on extension and when the patient put his forearm behind his back.

On examination a swelling 3 by 1.5 cm., was observed over the lateral aspect of the right elbow joint. This swelling was slightly fluctuant and tender. Extension of the elbow was more painful than flexion and was limited to 170 degrees, 5 degrees less than on the opposite side. There was slight limitation of supination.

The roentgenogram (fig. 4) of the anteroposterior view of the right elbow showed a dense shadow 1.25 by 1 cm., just over the radiohumeral joint. It seemed to be in the soft parts. The shadow was also seen in a corresponding position in the lateral view.

Operation was performed on May 13, 1930, by Dr. Kleinberg, with the patient under gas and ether anesthesia. A 6 cm. incision was made over the posterolateral aspect of the right elbow joint, the swelling being in the center of the incision. The deep fascia was incised, and the swelling was found to be underneath the common

extensor tendons. These were incised, and a cyst wall was found intimately adherent to the external lateral ligament and to the capsule of the joint between the epicondyle and the radial head. When the cyst was dissected out, milky fluid escaped which on culture was negative. The cyst was removed without entering the elbow joint. There were a few calcareous deposits in the wall. The wound was closed in layers. Dr. Henry L. Jaffe made a report of the pathologic examination. The specimen consisted of a cystic structure measuring 2 by 1 by 0.5 cm. The wall was calcified. A piece of tendinous tissue was attached to the sac, and this tissue was also calcified. On microscopic examination (figs. 6 and 7) the wall of the bursa was observed to



Fig. 4.—Roentgenogram of elbow in case 5. There is an irregular dense shadow over the radioulnar joint. This is seen in the anteroposterior and lateral views, and represents a calcified radioulnar bursa.

be thickened and composed of a thick layer of inflammatory tissue. The surface lining was for the most part destroyed, though in places the typical synovial-like lining could be observed. The granulation tissue of the lining membrane contained large irregular deposits of calcareous material, staining deep blue with hematoxylin. The calcific material was surrounded by and embedded in inflammatory tissue made up of numerous epithelioid cells, and the inflammatory tissue contained foreign body giant cells that had phagocytosed calcific material.

The diagnosis was calcified radiohumeral bursa.

May 21, 1930: The wound had healed by primary union. There was full range of motion in the elbow joint.

May 22: The roentgenogram (fig. 5) showed absence of the shadow previously reported. The patient was discharged.

June 6: Extension, flexion and supination were complete, although there was some pain in flexion. There was no tenderness. Physical therapy was given.

September 5: There was full range of motion in the elbow, with no pain or tenderness.



Fig. 5.—Roentgenogram of elbow seen in figure 4 after excision of the radiohumeral bursa.

May 15, 1931: Twelve months after operation, there were no symptoms or signs.

CASE 6.—Tennis elbow in a telephone operator caused by calcified radiohumeral bursitis. Patient treated by physical therapy and rest. Gradual disappearance of shadow in roentgenogram. Results observed for five and a half years.

M. N., an Irish woman, aged 24, single, who worked as a telephone operator, was admitted to the outpatient department of the Presbyterian Hospital on Jan. 16, 1926. She complained of stiffness and swelling over the outer aspect of the left elbow, which appeared four days before admission. Her work as a telephone operator for several years necessitated her suddenly flexing and extending her elbow



Fig. 2. Photomicrograph of the wall of the x-rayed fungus in case 2. The fungus thins is extremely flattened and bare rounded masses of thin stratified calcareous material are observed. Abundant (14).

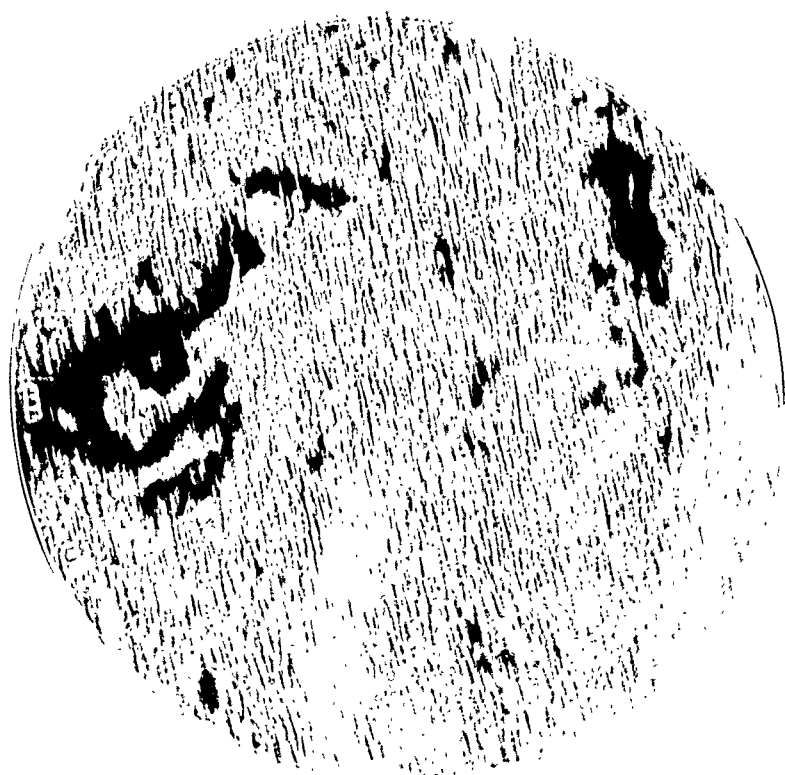


Fig. 3. Photomicrograph of the wall of the x-rayed fungus in case 2. The fungus thins is extremely flattened and bare rounded masses of thin stratified calcareous material are observed. Abundant (14).

in plugging in the wire. The day after her trouble began, the pain was sharper and the swelling increased. She had extreme weakness of the left hand so that she could not do her work and could not lift anything. Two nights prior to admission the pain in the left elbow kept her awake.

Examination of this elbow showed a slight swelling just beneath the epicondyle over the radiohumeral joint. There was exquisite localized tenderness. The grip of the left hand was very weak, and the pain in the outer aspect of the elbow was increased by flexion of the fingers with the wrist in flexion. Sudden extension of the elbow also produced pain.

A roentgenogram of the left elbow (fig. 8 *A*) showed a thin, moderately dense shadow extending from the lateral margin of the head of the radius to the epicon-



Fig 8.—Roentgenograms of elbow in case 6. In view *A*, note the narrow shadow over the radiohumeral joint. This represents a calcified radiohumeral bursa. *B*, taken two years later. There is absorption of the calcium deposits with a complete disappearance of the shadow. Rest and physical therapy were used.

dyle. The shadow looked like calcification in the soft tissues, probably in the radiohumeral bursa.

The diagnosis was acute radiohumeral bursitis.

The patient's arm was placed in a sling, and treatment consisted of rest, baking and the administration of salicylates. In four days there were less pain and swelling. In seven days the swelling was practically gone, the extremity could readily be used, and the hand grip was stronger. In eleven days she had pain over the lateral aspect of the elbow by flexing the fingers with the wrist in volar flexion, but none with the wrist in dorsal flexion. Swelling and tenderness over the radiohumeral joint persisted, and lifting with the left hand in supination was a little

difficult. In fourteen days she was doing her usual work, but the swelling and slight tenderness over the radiohumeral joint were still present. In seventeen days she had no pain, but the swelling and tenderness persisted. She lifted objects easily, and had a good hand grip. In twenty-two days all the symptoms and signs were gone.

One year after treatment there were no symptoms or signs; two years afterward there was no disability and only slight tenderness over the radiohumeral joint. A roentgenogram (fig. 8 *B*) showed a very faint shadow at one angle of the previous shadow. Three and a half and five and a half years afterward there were no symptoms or signs.

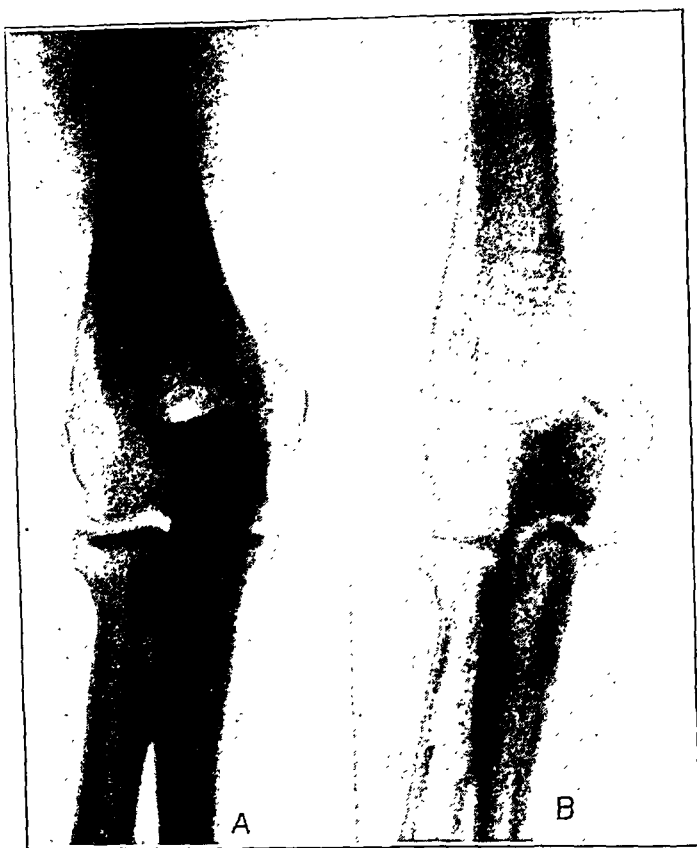


Fig. 9.—Roentgenograms of elbow in case 7: In view *A*, note the shadow over the epicondyle and radiohumeral joint. This represents a calcified radioulnar bursa. *B*, taken eleven months later. The shadow has disappeared owing to absorption of the calcium deposits. Rest and physical therapy were used.

CASE 7.—Tennis elbow caused by calcified radioulnar bursitis, the result of direct trauma. Positive roentgenographic findings. Absorption of the calcium salts within eleven months and disappearance of symptoms and signs. Patient treated originally by rest and physical therapy.

S. T., an American corset fitter, aged 37, was admitted to the outpatient department of the Hospital for Joint Diseases on June 20, 1930, complaining of pain in the right elbow and loss of power in the right forearm and hand. About a year prior to admission the outer side of her right elbow was struck by a swinging iron gate. Since then she had had intermittent pain in the elbow, which had increased

in intensity in the last few days. On examination there were swelling, heat and exquisite tenderness over the right epicondyle. Extension of the elbow was possible to 170 degrees and flexion to 90 degrees. Pronation and supination were complete. The power of the hand grip was greatly diminished.

The roentgenogram (fig. 9 *A*) showed a shadow extending from the epicondyle to the level of the radial head. It was in the soft parts and measured 2 by 0.3 cm.

The diagnosis was calcified radiohumeral bursitis. The patient was treated with a cock-up splint, rest, baking and massage for about a week, with only slight improvement. She then removed the splint and began treating her elbow by immersing it alternatingly in hot and cold water. The pain was not severe enough



Fig. 10.—Roentgenograms of elbow in case 8: In view *A*, note the oval shadow over the epicondyle. This represents a calcified bursa. *B*, taken ten weeks later. Note the diminished density of the calcified bursa.

to keep her awake. She was subsequently treated by her own physician for one week with diathermy. The pain and disability lasted for about five weeks, and at the time of this report, one year later, she stated that she has had no recurrence of the trouble, and no abnormal physical signs could be elicited.

On May 6, 1931, eleven months after treatment, the patient had had no trouble referable to her elbow. Function was complete, and there was no point of tenderness. A roentgenogram (fig. 9 *B*) of the elbow showed disappearance of the shadow shown in figure 9 *A*.

CASE 8.—Tennis elbow caused by a calcified bursa over the epicondyle in a squash tennis and golf player, the result of direct and indirect violence. Positive

roentgenogram. Disappearance of symptoms and signs in three weeks under physical therapy and beginning absorption of the calcium deposit in ten weeks.

H. B., an American executive, aged 47, consulted Dr. Fordyce B. St. John on Feb. 25, 1931, complaining of lameness and pain in the right elbow of two weeks' duration. He had played squash for several years, and during games struck his right elbow against the walls of the court repeatedly. He also played golf and had just spent a week skiing, using a pole with his right hand. A sharp nonradiating pain in the right elbow, which appeared on motion, and gripping movements of the hand developed. The elbow felt stiff on arising in the morning, and there was difficulty in complete extension.

Local examination showed no swelling, but there was tenderness over the epicondyle. The pain in the outer side of the elbow was increased by extension, which was limited to some extent. The hand grip was weaker than on the opposite side.

Roentgenograms of both elbows showed a slight hypertrophic reaction on the coronoid process and around the head of the radius on the right side (fig. 10 A). Within 5 mm. of the margin of the right epicondyle there was a small oval shadow of the density of calcium which was probably due to a deposit of calcium in the soft tissues. The articular space was not narrowed, and the density of the bones was unchanged.

The patient was referred to Dr. Norman E. Titus, who used the following physical therapy in the region of the epicondyle: radiant light, grounded autocondensation (localized high frequency) and the static brush discharge. The treatment was carried out eight times between March 31 and April 21. In two and a half weeks after the initial therapy the patient played golf without pain, and in six weeks he was using his extremity without any symptoms or signs. A roentgenogram (fig. 10 B) taken ten weeks after treatment began showed diminished density of the shadow seen in figure 10 A.

SUMMARY

1. An inflammatory involvement of the conjoined tendon at the epicondyle or of a structure in close proximity to it may produce the clinical syndrome known as tennis elbow. One of these structures is the radiohumeral bursa, the anatomy of which is discussed.

2. It is recommended that in all cases of tennis elbow a roentgenogram be made in order to try to visualize an osteitis of the epicondyle or a pathologic and distended radiohumeral bursa. The visualization of the latter condition depends on the character of the fluid contained or of the deposit in the wall. The presence of calcium salts produces a shadow.

3. Eight cases of radiohumeral bursitis are reported in which excellent results were obtained with different types of therapy. Five patients were males and three females. Direct trauma produced the lesion in two cases, indirect trauma in three, combined direct and indirect trauma in two and a questionable trauma in one. Swelling over the bursa was present in five cases, and there were positive roentgenographic findings in five. The operative finding in one case was a calcified radiohumeral bursa, in which the pathologic process is discussed.

In three other cases the spontaneous absorption of calcium deposits was noted. In the remaining four cases, manipulative rupture of the bursa was the method of treatment used.

4. Radiohumeral bursitis, especially in the presence of swelling, is frequently the cause of tennis elbow. Prompt relief may be expected from rupture of the bursa by firm digital pressure applied over the epicondyle and radiohumeral joint. When this procedure is very painful, a general anesthetic is advisable.

5. Operative therapy is not recommended unless conservative therapy fails to relieve prolonged or recurrent pain and disability.

DIVERTICULOSIS OF THE APPENDIX

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There are relatively few reports in the literature of cases of diverticulum of the appendix. This may indicate that it is a rather rare condition, or that it is considered of little clinical importance. It is my purpose to add evidence concerning the frequency of this condition and to emphasize the possible clinical significance of diverticulum of the vermiform appendix.

The frequency of such diverticula is not well established, and there is considerable difference of opinion among authors who have written on the subject. The frequency with which they are found depends largely on the care with which all appendixes are examined. So many appendixes are examined that they are of little interest to pathologists and clinicians in many instances. True diverticula with all the coats of the appendix appear to be rare, and it is probable that it is this type to which Kaufmann¹ refers when he says that "Diverticula are among the rarest of rarities." False diverticula appear to be more common and are spoken of as evaginations, herniations and protrusions of the mucosa and submucosa through defects in the muscularis. Most authors writing on this subject express the belief that these defects are more common than the number of reported cases would indicate.

After a thorough review of the literature up to 1907, Herb² found only 25 cases reported. Stout³ stated the belief that the condition is rather common. In one year he found 5 cases at the Presbyterian Hospital, New York, among 264 appendixes examined, though during the previous ten years at the same hospital only a single case was recorded. MacCarty and Magarth⁴ found 17 cases in 5,000 appendixes ;

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1. Kaufmann, Edward: Pathology for Students and Practitioners, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 2, p. 822.

2. Herb, Isabelle: Diverticulum of the Appendix, Tr. Chicago Path. Soc. 7:94, 1907.

3. Stout, A. P.: A Study of Diverticulum Formation in the Appendix, Arch. Surg. 6:793 (May) 1923.

4. MacCarty, W. C., and Magarth, B. F.: Clinical and Pathological Significance of Obliteration, Carcinoma, and Diverticulum of the Appendix, Surg., Gynec. & Obst. 12:211 (March) 1911.

5. Chase, W. H.: Three Cases of Diverticulum of the Appendix, Canad. M. A. J. 17:416 (April) 1927.

Chase,⁵ 3 cases in 394, and Moschcowitz,⁶ 4 cases in 1,500 appendixes. From these reports the frequency varies from 0.28 to 1.9 per cent.

The following points are most frequently mentioned as etiologic factors in the development of diverticula: (1) a weak point in the wall along a larger vessel, where there may be an accumulation of fat or atrophy of the muscle; (2) destruction of the muscle following a local inflammation; (3) increased tension within in chronic constipation; (4) weakening of the wall with old age, and (5) traction from without by adhesions.

Diverticula vary in size from 3 to 5 mm. in width, and they are rarely larger than 1 cm. They occur more often in the distal portion and along the mesenteric side. Their frequent occurrence in the mesentery probably explains the fact that many are not found in the routine examination of the appendix. In most cases there is one diverticulum, though from two to five have been reported in a few instances. Pack⁷ reported a case in which there were thirty-six separate diverticula.

During the past thirty months, all appendixes removed surgically and post mortem have been examined carefully for diverticula, after they were hardened in a diluted solution of formaldehyde U.S.P. (1:10) for from twenty-four to forty-eight hours. It is difficult to find them in the fresh specimen, and the fat of the mesentery must be carefully resected to reveal them in many cases. A large number of the perforated appendixes are no doubt due to rupture through a diverticulum. It is not easy to demonstrate them in perforated appendixes, especially if operation is delayed many hours after the rupture. I have found three cases in which perforation occurred through a diverticulum. Of course, it is well known that most cases of perforation of the appendix are associated with a concretion in the lumen, but in those occurring without the fecal concretion one may be able to demonstrate the diverticulum.

Since perforation of the appendix is frequently associated with a diverticulum, the study of diverticula of the appendix is of considerable importance. For this reason it seems desirable to give brief abstracts of the clinical findings and the essential anatomic changes occurring in the following cases of diverticulum of the appendix.

REPORT OF CASES

CASE 1.—Mr. L. C., aged 34, had a varicocelectomy in 1916. He had had what he called "spells of indigestion" for the past year. The present illness began two weeks previous to admission with general abdominal distress which was worse

6. Moschcowitz, Eli: Pathologic Diagnosis of Diseases of the Appendix Based on Study of 1500 Specimens, *Ann. Surg.* **63**:697 (June) 1916.

7. Pack, G. T., and Scharnagel, I.: Diverticulosis of the Appendix, *Am. J. Surg.* **5**:369 (Oct.) 1928.

than usual, and the patient called in his physician who noticed tenderness in the lower right quadrant of the abdomen, but there was no fever. There was no nausea or vomiting, and after a few days of rest in bed and a very light diet the patient felt much better. But the pain and tenderness in the region of the appendix remained. Two days before entering the hospital, he had another attack of abdominal distress, and there was no improvement the next day. The condition gradually became worse, and he entered the hospital with a temperature of 99.8 F. and a white cell count of 9,900. There was no nausea or vomiting. The appendix was 7 cm. in length and 0.9 cm. across. The central portion was slightly enlarged. In the middle portion the serosa was rough and congested. There was an apparent cyst 9 mm. in width in the mesentery of this region. Microscopically, the cyst was lined with mucosa and connected with the lumen of the appendix. There were many leukocytes scattered throughout the wall of the appendix in the middle portion and in the wall of the diverticulum. There was considerable scarring of the sub-

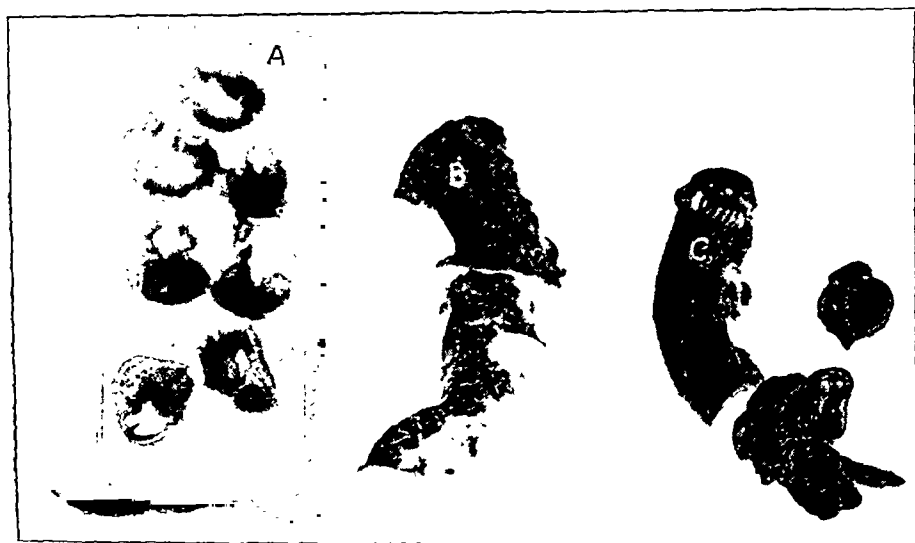


Fig. 1.—A (case 1) shows a cross-section of the diverticulum; B (case 2), gross view of diverticulum, and C (case 3), gross cross-section of diverticulum opposite the mesentery.

mucosa and the circular muscle layer of the distal half of the appendix. A cross-section of this diverticulum is shown in figure 1.

CASE 2.—Mrs. M. H., aged 67, had had an intermittent fever at the age of 14 which was called typhoid-malaria. She had had constipation for several years, and had experienced abdominal distress of an indefinite nature for the eighteen months previous to admission. When she entered the hospital it was found that she had a fever of 102 F., a white cell count of 18,700 and considerable pain and tenderness in the lower right quadrant of the abdomen. She was nauseated but did not vomit, but vomiting had occurred the day before admission; at that time the distress was most marked in the epigastrium. The appendix was removed, and a drain was left in the wound because of local peritonitis.

The appendix was 8 cm. in length and 1 cm. in width in the proximal half and 0.8 cm. in the distal third. A small piece of omentum was adherent to the distal end. Six diverticula were found in this appendix, all but one of which were

in the mesentery and in the distal half. The largest one was 6 mm. in width and projected 4 mm. from the serosa; it was 2 cm. from the proximal end and on the anterior side of the appendix. The serosa covering this was as thin as paper. Another diverticulum almost as large was present in the mesentery near the middle of the appendix. The others were smaller; they are shown in figures 1 and 2. Microscopically, there was considerable scarring and slight fatty infiltration of the submucosa of the distal third and considerable scarring of the muscularis of this part. There were many leukocytes in the wall and the mesentery of the proximal half of the appendix. Slight necrosis of the wall of the larger diverticulum in the mesentery near the center was noted. This was a case of acute inflammation of a previously scarred appendix, and it would require little necrosis or pressure to rupture through the larger diverticula.

CASE 3.—Mr. C. W., aged 50, had been troubled with constipation for years. Hemorrhoids and a rectal fistula were removed two years previous to admission. One week before admission he had moderate pain in the abdomen without nausea. The physician found tenderness in the lower right quadrant, but there was no fever. He seemed to improve until the evening prior to admission, when he became much worse. He entered the hospital the following morning with a fever of 99.4 F. and a leukocytosis of 15,000, but there was no nausea. There was marked tenderness over McBurney's point. The appendix was 7 cm. in length and 1 cm. in width. There was a diverticulum 1.5 cm. from the distal end in the antimesenteric region. Microscopically, there was acute inflammation of a considerably scarred appendix. The inflammation was most pronounced in the distal portion. Figure 1 shows the gross appearance.

CASE 4.—Mrs. M. A., aged 44, had had constipation for many years and many attacks of pain and distress in the lower part of the abdomen which were relieved by active catharsis. Two weeks before admission, a severe attack, with nausea but without emesis, occurred. At that time, the white blood count was 14,000, but there was no fever and only moderate tenderness over McBurney's point. At the time of operation, there were no particular complaints except slight tenderness in the lower right quadrant. The uterus was retroverted and fixed by adhesions to the rectum and broad ligament. There were many firm adhesions involving the appendix, fallopian tubes and ovaries. The appendix was 5.5 cm. in length and 0.8 cm. in width. There was a diverticulum in the mesentery 2.5 cm. from the distal end; it was 3 mm. in width and projected out 2 mm. There was considerable diffuse scarring of the appendix but no acute inflammation. Figure 2 shows the gross appearance.

CASE 5.—Mrs. L. W., aged 29, had what seems to have been an attack of appendicitis about a year prior to admission, but she had no further trouble. The present illness began the afternoon before she entered the hospital, with pain in the epigastrium followed in a few hours by nausea and vomiting. The physician noticed no tenderness or rigidity of the abdomen, and there was no fever. The next evening the pain and distress were much worse, and when the patient entered the hospital she was nauseated and vomiting; the temperature was 101.2 F. and the leukocyte count, 9,800. The surgeon found that there was no distention of the abdomen, but there were some rigidity of the right rectus muscle and marked tenderness over McBurney's point. The appendix was retrocecal and kinked by adhesions at less than a right angle near the junction of the middle and distal third. It was an angry red, and a drain was left in place.

The appendix was 5 cm. in length by 8 mm. in width. There was a diverticulum into the mesentery 1 cm. from the distal end. It was filled with pus, and the infection had spread beyond the limiting membrane of the diverticulum. There was no necrosis of the muscle fibers in this region or of the mucosa of the appendix. The gross structure is shown in figure 2.

CASE 6.—Mr. C. E., aged 30, entered the hospital with a fever of 99 and a white cell count of 17,400. The history stated that he had always been well. The present illness began on Sept. 29, 1930, with pain in paroxysms all over the abdomen. There was no nausea, but the patient thought that he had fever. His appetite was fair. The condition continued to get worse, and the patient saw his physician on



Fig. 2.—A shows each of the six diverticula that were incised in case 2; B (case 4), part of the appendix and the diverticulum; C (case 5), perforation through diverticulum into the mesentery; D (case 6), the mucosa bulging through the wall after the diverticulum was incised; E and F, diverticula in the mesentery. In E (case 7), the dark nodule to the right near the distal, incised end is the diverticulum, through which perforation occurred. F shows perforation through an apparent diverticulum of the mesentery.

October 2. At this time there was nothing definite, and the patient was advised to apply ice to the lower part of the abdomen. The pain became worse that night, and the next morning had become localized in the lower right quadrant. The surgeon found abdominal rigidity and tenderness over McBurney's point.

The appendix was 7.5 cm. in length and 1 cm. in width, except for the distal 3 cm., which was 3 cm. in width. There were two diverticula in the mesentery: one was 1.5 cm. and the other 2.5 cm. from the distal end. The one that was 2.5

cm. from the end projected 5 mm. from the appendix and was 5 mm. in width. It was covered with a very thin membrane on which there was an inflammatory exudate. The other one projected very little from the appendix, but the mucosa was in contact with the serosa and the lumen was filled with pus. The condition was diagnosed as an acute inflammatory chronic appendicitis. Figure 2 shows the gross appearance.

CASE 7.—Mr. A. W., aged 64, had typhoid fever in 1886 and had what seemed to have been an attack of appendicitis in 1892. Since that time, he had had frequent attacks of pain and distress in the lower part of the abdomen, but no nausea. At such times, he was usually constipated and laxatives relieved him. The last rather severe attack occurred about a year before admission. The present illness

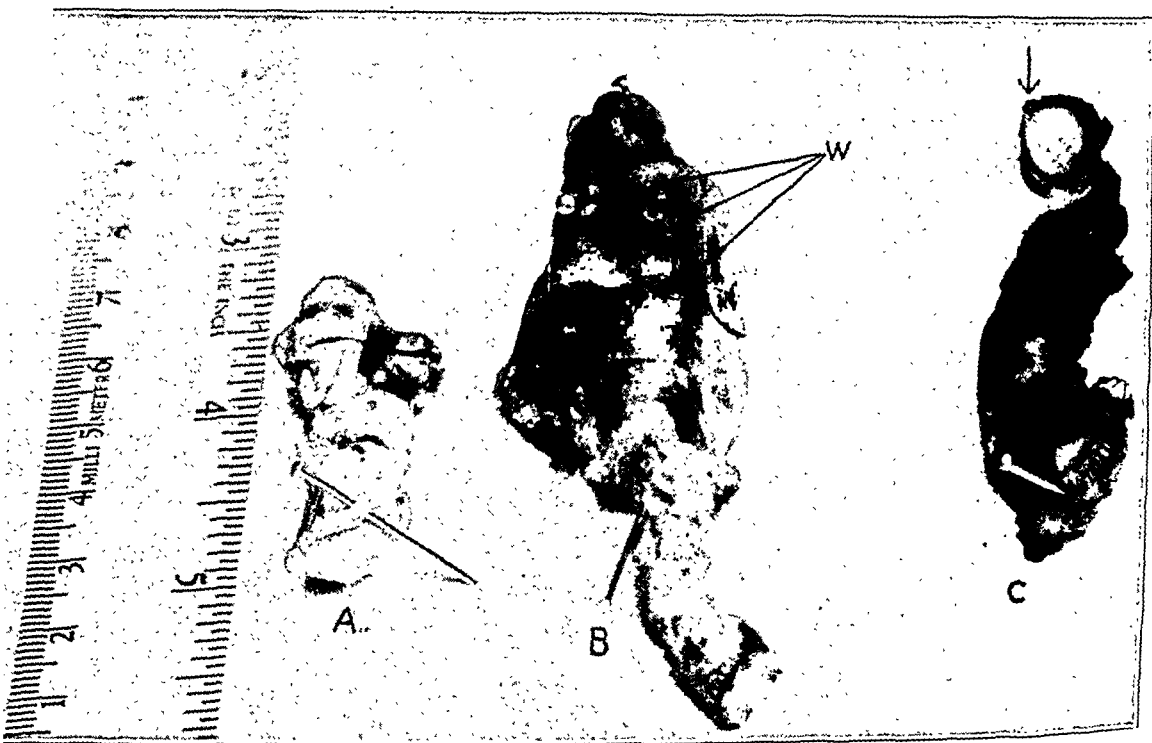


Fig. 3.—A, actual size of specimen in case 7, with perforated incised diverticulum; B, three wartlike structures (*W*) which are diverticula of antimesentery in case 9. The arrow in *C* indicates the diverticulum in case 6.

began three days previously with the usual distress in the lower part of the abdomen. He took laxatives and there were two movements of the bowels the next day. The distress continued, and he saw his physician who did not notice anything remarkable. On the morning of entrance into the hospital, however, when seen by his physician, the abdomen was rigid and the lower right quadrant was very tender.

At the operation the surgeon found an appendical abscess and left a drain in the wound. The appendix was 4.5 cm. long and 1.2 cm. wide. There was a perforation through a diverticulum 1.5 cm. from the distal end. This diverticulum was 5 mm. in width and projected 7 mm. from the appendix. Microscopically, there was no necrosis of the muscle fibers, and the mucosa came to the surface of the

appendix through the diverticulum. There was considerable chronic inflammation of the appendix as well as acute inflammation. Figures 2, 3 and 5 show the appearance of this diverticulum.

CASE 8.—Mr. J. H., aged 47, had typhoid fever at the age of 14. He had right inguinal hernia two years previous to admission to the hospital; it occurred following a fall, and healed in about a year by the use of a pad. About one year previously, he was in a runaway and fell from a wagon without sustaining any noticeable injuries. Early in May, 1928, he had rather severe pain and distress in the lower right quadrant of the abdomen, which were relieved by rest in bed and the use of laxatives. He had at least three such attacks, but had no more trouble during the summer. Early in November, the attacks recurred, and the use of laxatives and rest gave relief, but when he resumed work the pain returned. Late in November, a mass was felt by the patient in the region of the appendix. This mass seemed to disappear when the bowels moved freely. He first saw his physician on December 5. At that time, the physician noticed the mass, which was not particularly tender. There was no fever, and the patient never complained of nausea. His condition soon became worse, and on December 7, he had a fever of 101 F.,

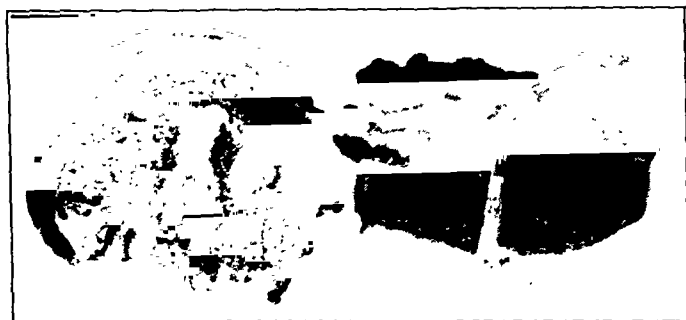


Fig. 4 (case 8).—Mucocoele of appendix with the proximal end enlarged and invaginated into the cecum causing gangrene of the cecum. A diverticulum is shown near the distal end, with very thin membranous wall.

obstipation and marked tenderness over McBurney's point. The diagnosis made by the surgeon before operation on December 8 was appendical abscess.

The appendix was 9 cm. in length. The proximal end was blackish and consisted of a spherical mass 3.5 cm. in width. This portion had been invaginated into the cecum, and the cecum covering this had become gangrenous. The remainder of the appendix was 2.2 cm. in width. The lumen was about 7 mm. in diameter and was filled with a water-colored gelatinous material. The lumen of the proximal portion was about 3 cm. in diameter. The proximal end of the lumen was obliterated and could not be found. There was a diverticulum of the mesenteric side near the distal end of the appendix. The diverticulum was 1.5 cm. wide, and projected 1 cm. from the appendix. Its wall was almost as thin as paper and seemed to be under considerable tension. Figure 4 shows the gross structure.

CASE 9.—Mr. J. A., aged 48, had always been constipated. He had been troubled with gas in the stomach and intestines for about three years and for this had had the tonsils removed. He had also had pain and soreness in the lower right abdominal region for about two years at irregular intervals. The present trouble began on March 15, 1931, with rather severe pain in the lower right quadrant,

which persisted until the next day, at which time he saw his physician who prescribed a cathartic; but the patient was too busy to get the medicine, and the following morning the pain was relieved by a spontaneous movement of the bowels. On March 21, the pain recurred, and he took two tablespoonfuls of castor oil. The next day the pain was worse, but he continued to work almost until evening, when he saw his physician and was brought to the hospital. He had no nausea and did not vomit. When he entered the hospital, the white cell count was 10,100 and the temperature was 102 F. There were considerable rigidity and tenderness over McBurney's point. At the operation a perforation was found through the mesentery near the distal end, with local peritonitis. A drain was left in place. When the patient went home the twenty-first day there was still a little drainage.

The appendix was 7 cm. in length and 1.2 cm. in diameter, except for the proximal 2 cm., which was 8 mm. in width. The fat of the mesentery was about



Fig. 5.—*A* (case 7) indicates cross-section showing the mucosa perforated and extending through the wall; *B* (case 9), cross-section of perforation through diverticulum at 1 and antimesenteric diverticulum at 2.

2 cm. in width. There was a perforation through the wall and through the fat 2 cm. from the distal end. This perforation occurred through a defect or diverticulum of the wall. There was another diverticulum near the middle in the mesentery, and there was considerable inflammation of the fatty tissue around it. There were 3 wartlike structures on the antimesenteric serosa near the distal end, which were also diverticula. The lumen of the appendix was small and contained a purulent fluid (figs. 3*b* and 5*b*).

Microscopically, there were considerable fatty infiltration and scarring of the submucosa. There was also moderate proliferation of capillaries and connective tissue in the submucosa. There were leukocytes throughout the wall and many in the mesenteric fat around both diverticula. A diagnosis of acute appendicitis with perforation through a mesenteric diverticulum of a chronically diseased appendix was made.

COMMENT

The clinical significance of diverticulosis of the appendix has apparently been underestimated. Beer⁸ has said that prognostically such diverticula are of little importance, since the appendix itself is a diverticulum. Gardham, Choyce and Randall⁹ likewise expressed the belief that the main clinical interest lies in the relation of these pouches to pseudomyxoma peritonaei. There is some truth in this, but pseudomyxoma peritonaei is rare and may develop from cystic ovaries. In case 8 pseudomyxoma peritonaei might have developed had there not been such early involvement of the cecum or had the diverticulum ruptured. Pseudomyxoma peritonaei is a rare complication of diverticulum of the appendix as compared to acute inflammations and the serious condition of perforation.

Of the nine cases described here, one occurred in a mucocele of the appendix, and in three perforation through a diverticulum occurred. All except one were found in cases of acute appendicitis. In six there was a single diverticulum; in one there were two diverticula; in another, five, and in the other, six diverticula. In five cases, the diverticulum was in the mesentery; in two cases they were antimesenteric, and in two others they were in both locations. In six cases the diverticulum was in the distal half. The age of the patients varied from 30 to 67, and six were in men. There was a history of typhoid fever in three cases. In only one case was there no history of a previous attack or of previous intestinal disturbances. However, in this case there was microscopically considerable scar tissue in the submucosa and some scarring of the circular muscle fibers. There was no histologic evidence of a previous disorder in only one case, and in this one there was a history of a previous attack. In four cases there was an acute inflammation of a scarred appendix, and one diverticulum occurred in such an appendix. There was chronic inflammation as well as acute inflammation in three cases.

The presence of diverticula in an appendix may explain how in recurring or subacute appendicitis there may suddenly be perforation with relatively few characteristic symptoms. It is to prevent such sudden or unexpected perforations that many so-called chronic appendices are removed. Most of the cases of diverticulum of the appendix that

8. Beer, Edwin: Pathologic and Clinical Aspects of Diverticulosis, *Am. J. M. Sc.* **128**:135, 1904.

9. Gardham, A. J.; Choyce, C. C., and Randall, M.: Diverticulosis of the Appendix and Pseudomyxoma Peritonei, *Brit. J. Surg.* **16**:62 (July) 1928.

have been reported have been found in acute appendicitis. It is not easy, however, to prove or disprove that in many cases acute perforations occur through diverticula. It is much easier to demonstrate diverticula in appendixes that have not perforated.

CONCLUSIONS

Diverticula of the appendix are more frequent than the reports in the literature would indicate.¹⁰ Nine cases with brief descriptions are reported in 661 appendixes examined during the past two years. The presence of a diverticulum in an appendix is of much more importance clinically than it has been considered to be by most writers reporting such cases. It appears that diverticula are more often than is realized the cause of sudden or unexpected perforations in so-called chronic appendicitis or recurring and acute appendicitis.

10. Since this article was sent to the publishers 4 additional cases of diverticula have been found in 209 appendixes.

DUPUYTREN'S CONTRACTION

WITH A NOTE ON THE INCIDENCE OF THE CONTRACTION
IN DIABETES

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The purpose of this paper is to call attention again to an interesting progressive surgical condition of the hands; the etiology is obscure; the diagnosis is frequently confused with contraction of the flexor tendons, and the treatment is often unsatisfactory. This report is based on a review of the literature and on a study of 40 cases heretofore unreported. In addition to this series, we shall also consider the cases of a group of 6 patients found in the examination of 200 patients in the diabetic clinic, who did not come to the clinic for surgical treatment.

This deformity was first described by Plater in 1610 and in 1808 was alluded to again in the surgical lectures of Henry Clive. In 1818, in a lecture on dislocations of the fingers, Sir Astley Cooper stated:

A toe or finger is sometimes thrown out of its natural position by the flexor tendon and theca, or even the palmar fascia becoming contracted . . . but when a thickened band of fascia appears to be the cause of the contraction, it may easily be divided by a pointed bistoury introduced through a very small wound in the integument. The finger should then be extended and kept in this position by a splint.

Dupuytren's contraction is the name applied to a permanent flexion of one or more of the fingers due to a contraction of the palmar aponeurosis and its digital prolongations.

From the scientific standpoint, there is a strong tendency in nomenclature to do away with the names of the surgeons who first described clinical entities; in spite of this there are some conditions to which the names of the investigators are tightly forged.

In 1831, Dupuytren's original and classic description of the true nature of the permanent retraction of the fingers consequent on a

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condition of the palmar aponeurosis, backed by actual dissection in such a case, proved the correct pathology of the disease and immortalized his name.

Dupuytren observed a patient with this contraction for a long time, and when death occurred was fortunate in securing the privilege of dissecting the hand and arm. The whole skin was removed from the palm of the hand, and the folds and wrinkles that had been present disappeared. He laid bare the palmar aponeurosis and was astonished to perceive that it was tense, contracted and shortened, and that from its lower portion proceeded cords that extended to the sides of the affected fingers. When he cut the prolongations to the sides of the fingers, the contraction ceased immediately, and the slightest exertion extended the phalanges perfectly. The tendons were intact; the sheaths had not been opened. To remove doubt and to conquer all objections, Dupuytren exposed the tendons. They were of normal size and movement, and their surfaces were smooth and glistening. He carried the examination still further: the surfaces of the joints and articulations were also normal. Hence it was natural for him to conclude that the commencement of the disease was a result of the unusual tension of the palmar aponeurosis, and that this tension arose from a contusion of the aponeurosis as a consequence of the too violent and too long continued action of a hard body on the palm of the hand.

ANATOMY OF THE PALMAR APONEUROSIS

Surgical Anatomy.—A careful dissection of the palm and fingers first reveals a dense layer of fibro-areolar tissue, the superficial palmar fascia. The fibers are thin but strong and form a web, the meshes of which are filled with fatty tissue, resembling the soles in this respect. The superficial palmar fascia is a continuation of the palmaris longus tendon and is divided into three parts. It consists of a thick triangular central part and two thin lateral portions. The lateral parts of the palmar fascia are thin, fibrous layers which on the radial side cover the thenar eminence and on the ulnar side, the hypothenar eminence. The central portion occupies the middle of the palm and spreads out like a fan from the wrist toward the fingers. This is the most important part of the fascia and is of great strength and considerable thickness. In its passage through the palm as it approaches the fingers, it divides into four distinct bands (the pretendinous bands, or *longuettes prétendineuses* of Poirer), which are chiefly inserted into the deep layers of the skin just proximal to the webs of the fingers. The continuations of the pretendinous bands to the fingers make up the digital slips, one for each finger. Each digital slip is divided into three parts, the median process, which passes along the palmar surface of the finger and is

inserted into the skin as far down as the pulp of the last phalanx, and the two lateral processes, which surround the tendon sheaths and are inserted into the dorsal surface of the first and second phalanges.

Extending from the central triangular part of the palmar aponeurosis are many short vertical and oblique fibers arranged in fairly longitudinal lines, which unite the fascia to the deeper layers of the skin. These short fibers are of particular interest, for through this attachment between the palmar aponeurosis and the skin is produced the dimpling of the palmar skin, which is frequently the first sign of Dupuytren's contraction.

Microscopic Anatomy.—Microscopically, the palmar fascia consists of coarse bundles of dense fibrous tissue, which in places are connected with the corium by smaller fibrous bands crossing through the fatty

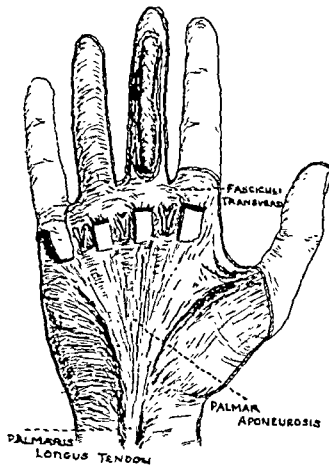


Fig. 1.—The palmar aponeurosis (superficial palmar fascia). Redrawn from Kanavel, Koch and Mason (*Surg., Gynec. & Obst.* 48:145, 1929).

layer that separates the fascia from the cutis. The fibrous fasciculi are arranged longitudinally and, in places also transversely. The fibrous tissue consists mainly of white fibers, among which are numerous exceedingly elongated connective tissue cells. Penetrating among and running along the fibrous bundles are minute blood vessels.

FUNCTION

The dense central portion of the palmar aponeurosis protects the underlying tendons, vessels and nerves from injury. It limits to a certain extent not only flexion, but more particularly, overextension of the fingers. The small, short fibrous bands that closely unite the fascia and the skin prevent the integument from being thrown into folds and from gliding to and fro during the various movements of the hand.

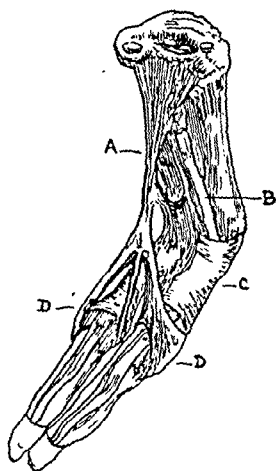


Fig. 2.—Dissection of Dupuytren's contraction of the middle and ring fingers showing the contraction to be caused by the palmar fascia. *A* indicates the contracted band of palmar fascia; *B*, the flexor tendons lying close to the bones and bound down along the first phalanges of the fingers by the dense tubular sheath (*C*) through which they pass; *D*, digital prolongations of palmar fascia extending to the articulation between the first and second phalanges in each finger. Note that the second and third phalanges remain in line, continuous with that of the first phalanx, which alone is flexed toward the palm of the hand; that is, the second phalanx is not bent on the first nor is any angle of flexion formed between the first and second phalanges. (Redrawn from Adams from his illustration of a specimen in St. Bartholomew's Hospital Museum.)

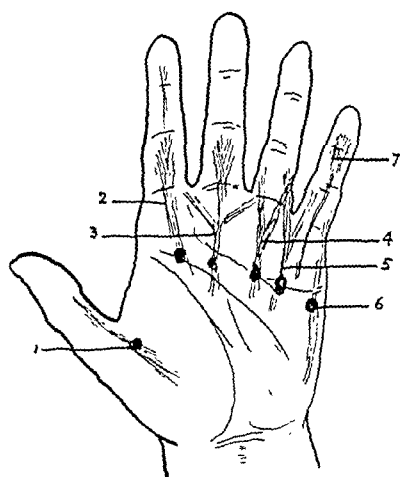


Fig. 3.—Diagram showing the types of abnormal fascia bands that may be found in Dupuytren's contraction. The position of the initial lesions over the heads of the metacarpal bones and opposite the flexion lines is indicated by the black spots. *1* indicates the thenar band; *2*, axial band extending to distal joint; *3*, axial band giving off lateral branches to the adjoining finger; *4*, axial band bifurcating to send branches to the sides of the finger; *5*, "interosseous" band bifurcating to join two adjacent digits and *6*, hypothenar band. The band is more developed at the distal than at the proximal extremity and leads to the contraction of the first or second interphalangeal joint, the metacarpophalangeal joint remaining free. This diagram indicates the possible extent of fascia involvement and gives an idea of the wide dissection that may be necessary in order to remove the contracted bands. (Redrawn from Anderson: *Deformities of the Fingers and Toes*, London, J. & A. Churchill, 1897.)

ETIOLOGY

While Dupuytren established the fact that the disease under discussion was due to a contraction of the palmar fascia, the etiology of this so-called minor surgical condition is as obscure today as it was in 1831.

The theories as to the etiology may be divided into four main groups:

1. External agencies: stress and oft-repeated trauma to the palm
2. Constitutional origin, with heredity playing a rôle
3. Combination of groups 1 and 2: constitutional predisposition plus trauma
4. Miscellaneous agencies

Group 1: External Agencies.—In his original lectures, Dupuytren stated that the cause of the retraction of the fingers had hitherto been unknown, and that it had been ascribed successively to a rheumatic or gouty condition, an external injury, a fracture, metastasis from a morbid cause, which sometimes occurs after inflammation of the sheaths of the flexor tendons, or to a kind of ankylosis. "We shall point out, however," he said, "that all these causes are unfounded." He favored the theory of trauma and stated that the disease appears principally in those who are obliged to use the palm of the hand as a point of support. Thus, for instance, the wine merchant and the hackney coachman were accustomed, the one to bore his hogsheads with a gimlet or to pile up his barrels and the other, to keep his whip constantly in action on the backs of his jaded ponies. Dupuytren also cited the case of a diplomat, who was particularly nice in sealing his dispatches. The condition also occurs in masons who grasp large stones, in farmers and in other persons of this type.

Both Kaern and Marwedel reported cases that occurred following trauma or injury to the palm. The former cited two cases: one developed following a machine gun wound and the other followed a penetrating wound caused by a nail. Marwedel cited the two following cases and said that Dupuytren's contraction may develop within a short time and may occur after a single injury. The first patient, a man aged 60, fell and subluxated the fingers of the right hand. A few weeks later, typical Dupuytren's contraction developed. The second patient, a man aged 24, suffered from the formation of slight abscesses on the flexor surface of the proximal phalanx of the middle finger of the right hand. Two months later Dupuytren's contraction developed.

In our own series, nine patients attributed the contraction to trauma, but this was difficult to prove. One of them, a chemist aged 45, gave a history of working with dyes for several years and of constantly using a short pestle, the end of which pressed against the palm of his right hand. He attributed the contraction to the use of this tool. However,

since relief from the contraction of the right hand has been obtained, the condition is developing on the left.

In 1929, Oller also discussed the question as to whether Dupuytren's contraction can be considered an occupational disease or due to trauma. He said that it is hard to show that Dupuytren's contraction does not result from slight, oft repeated trauma; however, there are four good arguments against this theory: 1. Among many million workmen who suffer hematomas and repeated trauma of the hand, there are very few cases of Dupuytren's contraction. 2. Many cases of Dupuytren's contraction occur in persons doing mental work. 3. The contraction is almost always bilateral, while the trauma is generally limited to the most active hand. 4. When Dupuytren's contraction is unilateral, it occurs almost always in the hand that works least.

Oller gave statistics confirming these statements, and reported three cases. The cases occurred in a pianist, a baker and a bricklayer; the latter had the contraction in the left hand and in both the others, the condition was bilateral. The baker had been working for thirty-one years without an anomaly, and the contraction began about three years after he retired. A large number of workmen in various trades were examined, and those who were exposed to constantly repeated trauma of the hands did not show higher percentage of Dupuytren's contraction than did the others. Therefore, as a rule, Oller does not think that Dupuytren's contraction is caused by either single or repeated trauma.

In 1912, as the result of a report of factory inspectors in Nottingham, England, the Home Secretary appointed a departmental committee to inquire into the causation of Dupuytren's contraction and the extent of its prevalence among lace workers in Nottingham. At the inquiry held by this committee, divergent opinions were expressed. Dr. Edgar Collis, one of the medical inspectors, was of the opinion that in all cases palmar stresses or pressures were the exciting causes. Sir Robert Jones thought that the cause was probably a predisposition, with palmar irritation as the exciting factor. Mr. Kenneth Black pointed out that the returns from medical practitioners showed fewer cases among the working class than among the nonworking class, and that of the 21,471 patients admitted to the Nottingham General Hospital from 1905 to 1911 inclusive, only 1 was admitted for Dupuytren's contraction.

Nichols, quoting from his two series of cases totaling 90, felt that on the whole, so far as histories are concerned, the facts observed are decidedly adverse to the supposition that the disease is essentially due to local traumatic causes. Other considerations opposed to the theory of traumatic origin are as follows:

1. The usual age of onset is after middle life, many years after the period of active labor begins.

2. The involvement is often bilateral. Byford collected 592 cases, and 294 were bilateral. In his own series of 38 cases, 25 were bilateral. In 50 cases reported by Nichols, 22 were bilateral. In our series of 40, 26 were bilateral.

3. The contracture is not limited to those who work with the hands. Keen, in a series of 133 patients, reported 74 as nonlaborers. In Black's 131 cases, 68 patients were nonlaborers. In 38 patients, most of whom were from a poor-farm, Byford reported 14 as nonlaborers. In our series, 20 or 50 per cent of the patients were not of the laboring class.

4. The left hand is affected about as frequently as the right, and the ring and little fingers are much more frequently affected than the radial half of the hand, which bears the brunt of labor to an equal, if not to a greater, degree.

5. If it is due to trauma, the disease should be much more common.

Group 2: Constitutional Origin, Hereditary Tendency.—The theory that the disease is a manifestation of some constitutional condition, such as gout or rheumatism, has been widely held, particularly by Keen, Adams, Anderson and others. Keen said that its cause lies deeper than any local influence, and that a constitutional condition such as gout or rheumatism, if sought for, will nearly always be found. He reported the history of gout in 95 of 148 cases, or 48 per cent. In our 40 patients, only 4, or 10 per cent, had gout or rheumatism. Adams and Anderson are in accord with Keen. The former agrees that the disease always depends on a constitutional rather than on a local cause. The latter feels that the earlier observers greatly exaggerated the importance of occupation, local irritation and trauma. Indeed, it appears to him that in persons in various callings that involve much rough treatment of the palms the condition is even less common than in those from the rest of the community. Little said that mechanical agencies, if really operative, can be regarded only as occasional determining or exciting causes. The essential or primary cause is a constitutional one, allied to the gouty or rheumatic diathesis. Black expressed the belief that eventually it will be recognized that the anomaly is due to a certain internal condition (possibly akin to gout or rheumatism) among persons of advancing age.

The investigations of Ledderhose on the clinical aspects of arthritis deformans have led him to the conviction that Dupuytren's contraction or fasciitis palmaris, as he calls it, is an integral part of the symptomatology of arthritis deformans, and, furthermore, that a patient who presents symptoms of arthritis deformans in any of the large joints or in the spine will also show evidence of characteristic changes in the palmar aponeurosis. He expressed the belief that there is a marked agreement between arthritis deformans and Dupuytren's contraction, in that both conditions frequently begin in youth, may remain latent

for a long period and after a long life have not progressed so far as to present pronounced deformation of the joints or marked contraction of the fingers. In our series of 40 cases of Dupuytren's contraction, only a single patient had arthritis deformans.

A search of the literature since the time of Dupuytren's original paper seems to indicate that in certain families that are perhaps constitutionally predisposed, whatever that may mean, the disease is more common than in families without this predisposition. Dupuytren himself does not mention the hereditary factor.

Sprogis traced Dupuytren's contraction through three generations of a certain family, and found 17 cases among 53 persons, only 2 of which occurred in women. Both he and Antonioli agree with Krogius that the latter's interpretation, namely, that the condition is an atavistic deficiency or developmental disease due to disorders of growth in the

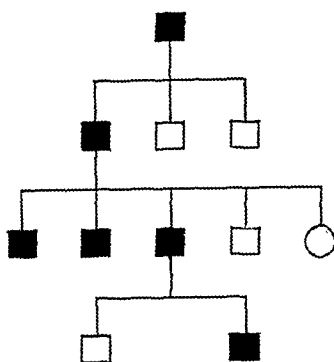


Fig. 4.—Chart illustrating the factor of heredity in Dupuytren's contraction in a family in which the condition appeared in four generations. The squares indicate males, the circles, females. The solid squares show occurrence of the contraction; the open squares signify its absence. Each horizontal line represents one generation. One of the sons in the second generation inherited the contraction. He married twice and had eighteen children, eleven boys and seven girls. Three of the eleven boys inherited the contraction. (Redrawn from Löwy: *Zentralbl. f. inn. Med.* **44**:51, 1923.)

superficial palmar muscles, is the one best adapted to reconcile anatomic findings with clinical data. Krogius further suggested that a satisfactory theory as to etiology must explain two common factors: its hereditary incidence and its symmetrical arrangement on the ulnar side.

Apert reported the observation of a family in which Dupuytren's contraction occurred in four generations. It affected only men, and it appeared earlier in each successive generation. This peculiarity was also observed by Löwy and Kartschikjan. The latter found the disease in five members of a family; the condition occurred only in the male line and spared the female members. Nippert also confirmed this observation. Apert noted that in this family a hereditary predisposition seemed to be the sole cause.

In the family tree reported by Löwy, the second son of the second generation died early in childhood, so it is not known whether or not he would have acquired this condition. The first son passed the condition on to the next generation. He had two wives and eighteen children, of whom the first three sons were affected by Dupuytren's contraction. The disease was then transmitted to the next generation by the third son, who had two children, both girls, the youngest being affected. Of the 5 persons who acquired the disease in this family, 3 were farmers, 1 a printer and 1 a carpenter. In the first three generations, the disease did not appear until after the fortieth year; the female patient in the fourth generation was affected in the twenty-fourth year. The disease appears to have a tendency to transmit itself earlier in each succeeding generation.

Hutchinson reports 3 cases in which there were family histories of the condition. In the first case, that of a patient 36 years old, the father and grandfather were also affected; in the second case, that of a patient aged 56, an uncle and a brother also had the condition; in the third case, that of a patient aged 55, the patient's mother also had Dupuytren's contraction.

In the 24 cases that McWilliams reported, only 2 patients gave a family history of the disease. In the series that Nichols reported, the family histories in most cases were too imperfect to afford reliable statistics as to the influence of heredity in the etiology of the disease. However, he was able to determine that in the 50 cases there were 11 patients whose parents had no contraction of the fingers, and in 3 cases a parent was known to have had such a contraction. In the 16 cases reported by Janssen, there was no evidence of heredity in a single case.

In our 40 cases, 5 patients gave a family history of the disease. Three of these cases occurred in women; in one case the grandmother and great grandmother had similar contractions; in another the father and brother had Dupuytren's contraction, and in the third, the mother had a similar contraction. One of the two men who gave a family history of the condition is a doctor, and both his father and grandfather, who were also doctors, had Dupuytren's contraction; the other patient, a clerk, aged 27, gave the history that his grandmother on his father's side, his father and a younger sister had Dupuytren's contraction. We believe that a family history of Dupuytren's contraction would be more common if accurate information could be obtained on this point.¹

1. Since this article was submitted for publication, an unusual and interesting history on "Hereditary and Dupuytren's Contraction" has been reported by J. S. Manson (*Brit. M. J.* 2:11 [July 4] 1931) in which the father and mother and their three sons had Dupuytren's contraction, but the daughters did not. As yet no sign of the deformity has appeared in the third generation of eight children, whose ages are now between 33 and 41 years.

According to Nippert, patients with Dupuytren's contraction inherit an increased tonicity in the sympathetic nervous system, and they suffer not only from a hyperexcitability of this system, but from a hyperexcitability of the peripheral nervous system. A positive Chvostek sign and a cathodal opening contraction below 5 milliamperes are considered the criteria for this peripheral hyperexcitability. Further stigmas in such persons, as given by Nippert, are decreased blood pressure (from 80 to 100 mg. of mercury systolic), a tendency to excitability and livid discoloration of the extremities. He concluded that Dupuytren's contraction is a disease symptom that occurs in the hypertonicity of the vegetative nervous system, and that it is inherited.

Group 3: Constitutional Predisposition Plus Trauma.—In 1923, Schubert stressed the observation that the disease involves the fourth and fifth fingers, the region of the ulnar nerve. It is remarkable, he said, that the disease occurs in every kind of condition of the ulnar nerve, for instance, in neuritis and diseases of the central nervous system, such as syringomyelia and tabes. The chief objection to this theory lies in the statistics of injuries during the war compiled by Coenen; among 37 cases of injury to the ulnar nerve, he did not observe a case of Dupuytren's contraction. In not one of our 40 cases did we observe this connection. "This, however," Schubert remarked, "only proves that a second factor must be present." This factor, according to him, consists in a constitutional predisposition to proliferation of connective tissue. An injury of the ulnar nerve is capable of causing a typical Dupuytren's contraction. These cases are rare but characteristic. He explains that the reason why Dupuytren's contraction is seldom observed in spite of frequent injuries of the ulnaris in practical life is found in the following fact: The real internal cause of the condition is a constitutional weakness of the connective tissue, and an external cause, such as injury to the ulnar nerve, leads to a typical Dupuytren's contraction only when it influences a constitutionally changed region. How far practical conclusions may be drawn from these theoretical conclusions for expert testimony as regards accident is shown by a case reported by this author. A person with a tendency to Dupuytren's contraction in the form of callosities in both palms showed true Dupuytren's contraction in the hand of the same side two and one-half months after a positively determined injury of the inner condyle of the elbow. Since the ulnar nerve is situated immediately back of the inner condyle, showing the consequences of injury in the form of bony deposits, it must be assumed that the nerve had been injured simultaneously with the inner condyle, and that this injury to the nerve must be considered as the cause of the rapid appearance of the disease. Schubert claimed that in his case the tendency to Dupuy-

tren's contraction had no doubt been present, and a causal connection between the injury of the elbow joint and the subsequent pronounced contraction must be considered as a manifestation of a latent disease due to the accident. Without the influence of the trauma, the disease would not have taken the same course. Perhaps it would never have led to any practically significant consequences. The author concluded his interesting theory by noting that up to the present, a connection between trauma and the genesis of Dupuytren's contraction has been considered only when the trauma has directly influenced the palm. It is of practical and theoretical significance that in several patients observed the injury had taken place in the shoulder and the elbow joint. This is further proof that in addition to the constitutionally caused local weakness of the connective tissue, the injury of the ulnaris has an important causal significance in the genesis of true Dupuytren's contraction.

Many years before Schubert, both Abbe and Nichols stated that the possibility of the nervous origin of Dupuytren's contraction was worthy of consideration. According to a theory of the former, the etiologic factors occurred in the following sequence: (1) a slight traumatism of the palm often entirely forgotten; (2) a spinal impression produced by this peripheral irritation; (3) a reflex influence to the part originally hurt, producing insensible hyperemia, nutritional disturbances of the tissues and new growth, shown in the contracting bands of fascia and occasional lesions of the joints resembling subacute rheumatism, and (4) through the tense contraction, a second series of reflex symptoms, neuralgias, general systemic disturbances and a reflection of the condition to the corresponding part of the opposite hand.

In a few of his cases Nichols noticed marked predilection for the ulnar side, prickling and tingling which he thought quite suggestive of the paresthesia of a nervous lesion, association with trophic lesions, such as syringomyelia and anterior poliomyelitis and the involvement of both hands. In a series of 50 cases reported by him, only 7 patients gave histories of having had nervous disorders. As previously stated, in our 40 cases, not one patient gave a history suggestive of nervous origin of the condition.

In 1927, Schubert again wrote an interesting paper on the practical importance in workmen's compensation cases of the connection between accidents and the development of Dupuytren's contraction. He observed that a direct connection between an injury affecting the palm and the genesis of true Dupuytren's contraction has as yet scarcely been determined. In practical expert testimony concerning accidents, such a direct connection should be rejected in the majority of cases. In certain cases in predisposed persons, however, an injury was able to cause the full development of a clinically symptomless Dupuytren's

contraction. Such examples prove that an indirect connection exists between trauma and the genesis of Dupuytren's contraction. Schubert said that the bilateral appearance of this contraction, its presence in persons doing mental work, and, on the other hand, its comparatively infrequent appearance in callings in which the tendon layer of the palm is used continuously are reasons for denying the etiologic connection between trauma and the genesis of the contraction. In the majority of cases, trauma should therefore be rejected as a direct cause of the disease, which requires compensation. He concluded, since it is impossible to prove that external causes alone are responsible for Dupuytren's contraction, this disease is by many authors considered as a classic example of a constitutionally caused condition. The reasons for this are the bilateral appearance of the disease and the often observed simultaneous presence of Dupuytren's contractions and *induratio penis plastica*. (The latter condition did not occur in our series.) "This must be interpreted as a constitutionally caused morbid hyperplasia of the connective tissue, appearing in different sites of the body."

Schubert expressed the belief that this constitutional tendency toward Dupuytren's contraction can be congenital. Grieg reported such a case in a boy 5 years old, the fifth child; the parents and the other children were healthy. The fingers of both hands were flexed in the palms; the thumbs were free and extended. There was no fixation of the palmar fascia to the skin. Grieg stated the belief that Dupuytren's contraction is due to an alteration in the normal processes of the palmar fascia passing along the anterior surfaces of the fingers and that there is no inherent impossibility that an exaggeration of these processes in utero could not produce this congenital abnormality.

In Keen's "Surgery," Lovett stated that congenital contraction of the fingers rarely exists as a flexion of the little finger of one or both hands, with possible involvement of the ring or other fingers. He considered the condition as hereditary, and that it is most often due to a shortening of the skin and fascia on the palmar surface.

We, too, feel that congenital contractions of the fingers are in no way related to Dupuytren's contraction, and quote the following paragraph written by one of us (Dr. Davis) in an article published elsewhere:

Congenital contractions differ from the Dupuytren type in that they are congenital, whereas Dupuytren's contraction is generally a disease of adult life; congenital contraction usually occurs in females, whereas in the Dupuytren variety the patients are most commonly men. In the congenital form the central portion of the palmar fascia and its lateral prolongations are never involved, consequently the first phalanx is never flexed, but is hyperextended. The skin is atrophied, but is seldom if ever indurated and lumpy, a condition always present in Dupuytren's contraction.

McWilliams also felt that a general predisposition to the disease must be present, and that, in a certain number of cases at least, local insults act not only as exciting causes, but also as continuing influences; for example, direct irritation of the palm, as from leaning much on a round-headed cane or from the constant use of an instrument such as an awl, in a person with some causative diathesis or otherwise constitutionally predisposed to the disease.

Group 4: Miscellaneous Agencies.—Under this heading are grouped, for the sake of convenience, other etiologic theories not discussed in the preceding paragraphs.

Byford, Ely and Tubby suggested that Dupuytren's contraction is frequently associated with and closely allied to rheumatism, and that it is probably due to bacterial action at some point other than in the palmar fascia. In 1913, Tubby examined many specimens for bacteria, both microscopically and bacteriologically, with negative results, disproving the theory that Dupuytren's contraction is due to an infection of the palmar fascia that enters through the sweat glands of the palm and causes a chronic septic lymphangitis. In his latest paper he expressed the belief that the contraction is a fibrositis or the local expression of some subtle change in the body metabolism. He felt that its frequent association with rheumatism and almost constant association with a source of infection suggest some relation to a low grade sepsis, particularly that arising from infections in the alveoli and gums. As arthritis deformans is more common in injured joints, or in those on which persistent strain has been thrown, the contraction appears in the palm that is exposed to trauma and irritation. Byford and Ely stated that they believe that the most common site of this focal infection is in the teeth. The latter found dental infection in all of his cases, and in the case of a medical student, aged 25, he found badly infected tonsils.

Unquestionably infection of the teeth and the alveolar process is frequently found in persons with Dupuytren's contraction; it must be remembered, however, that the majority of such patients are past middle age, and that they are often in poor circumstances and the teeth have had little or no care. On the other hand, oral infections are present in a vast number of people who do not have contraction of the palmar aponeurosis. Furthermore, in our own series a number of patients had perfect teeth and no infection of the throat or mouth.

However, it is possible that in cases in which there is a hereditary tendency plus trauma, infected alveoli or teeth may have an effect on the causation of the disease of the palmar fascia.

Both Wainwright and Léopold Levi expressed the belief that Dupuytren's contraction is a symptom of thyroid deficiency. The former, after treating several patients with thyroid extract, came to the conclusion

that "the *tertium quid* in Dupuytren's contraction is endocrine deficiency, although heredity and (in some cases) palmar traumatism may have also a certain influence in the causation of the condition." So far as our patients were concerned, the few whose basal metabolism was ascertained showed no evidence of thyroid deficiency.

Teschemacher found diabetes associated in 33 of 213 cases of Dupuytren's contraction; in reviewing the literature with this fact in mind, he found that Noorden discovered 4 cases of Dupuytren's contraction in 800 diabetic patients. In our series of 40 cases, 3 patients had a coincident diabetes.

Girdwood reported a case of Dupuytren's contraction in a miner with severe asthma and gave an unusual explanation as to the causation in that case. The patient was 40 years old; he had had asthma and bronchitis for fifteen years. On account of the expiratory dyspnea, he had to bring all his external muscles of respiration into play. In order to do this, he required a fixed point from which to work. This he obtained by pressing his hands firmly on the bedposts. It seems that this caused absorption of the palmar fat and the subsequent adhesion of the skin and fascia. Girdwood remarked that he had never seen a case of Dupuytren's contraction in a miner, and he had worked among them for fifteen years. Madelung seems to have had this same idea, for he attributes the disease to the disappearance of the fatty subcutaneous tissue, which exposes the deeper tissues to greater traumatic insults.

In this miscellaneous group, one of the most interesting theories was developed by some Frenchmen who came to the conclusion that Dupuytren's contraction is as much a mark of lead poisoning as any of the classic signs. In 33 cases they found only 9 patients who gave no history of working with lead. Eleven had no signs of lead poisoning, 13 had well developed cases of lead poisoning. Of the 9 who had not worked with lead, 1 was diabetic, 1 syphilitic, 2 had worked for a long time in metal and 4 others seemed to have alimentary intoxication. They examined 2 patients who attributed the condition to trench digging, and another who ascribed it to the breaking of a spade handle in his hand. Both patients were given pensions on the basis of these claims; however, one was a house painter and the other a printer; both had colic. In our own series of 40 cases, we had a patient who was a painter; however, he had none of the classic symptoms or signs of lead poisoning, and his father also had had Dupuytren's contraction. None of our other patients gave a history of working with lead.

Another theory is sponsored by Cokkalis, who found that in the early stages of development, small muscles are found in the hands and feet instead of connective tissue and fascial sheaths. He said that even in the new-born infant, the palmar aponeurosis contains striated muscle

elements. Therefore it must be regarded as a tendon structure of muscular origin. This theory is supported by the fact that similar changes are found also in the feet. He reported a case in which the contraction occurred first in both hands and a year later in the feet. In none of our cases have the feet been involved.

In 1885, Noble Smith stated that the etiology of Dupuytren's contraction had nothing to do with gout or rheumatism; he was impressed, however, by the rôle played by the palmaris longus muscle in the causation of the disease. In the last forty-five cases which he saw at the time of the report, he found the muscle tense and prominent in nearly every case. He thought that contraction of the muscle might be the initial morbid condition, and that by its constant action it irritates the fascia and so causes it to thicken and contract. If this is so, such a process would not preclude the formation of the contraction in some cases by irritation of the fascia locally. In fact, it seemed probable to him that in many cases local irritation first produces contraction of the muscle and subsequently helps to continue the irritation of the fascia, and that in the other cases the contraction of the muscle is the original cause. He stated that the contraction of the palmaris longus muscle demands more attention than it has hitherto received, and that when tense, it should be divided. He concluded that in the early stages of Dupuytren's contraction, tenotomy of this muscle might possibly stop the development of the disease by lessening or removing the constant irritation of the palmaris fascia. This theory is interesting, but so far as we know, such a procedure has not been tried.

Finally, the theory has been advanced that Dupuytren's contraction is always due to the pressure of a cervical rib. This may be true in rare instances, but in the vast majority of cases of cervical rib, Dupuytren's contraction is not present. We are told by F. H. Baetjer that approximately 50 per cent of all cases of cervical rib are bilateral, and that of the other 50 per cent (unilateral) about one half showed rudimentary outgrowths on the other side. We have often seen atrophy of the muscles of the thenar and hypothenar group in patients with cervical ribs, but have not yet observed Dupuytren's contraction in patients in whom cervical ribs are known to exist. In fact, since this theory was brought to our attention, we have had x-ray plates taken of patients with bilateral Dupuytren's contraction, and in none of them were cervical ribs found.

With these theories in mind and from our own observations, we agree with Nichols that the only conclusion as to etiology that seems warranted is that Dupuytren's contraction is of idiopathic origin; that it is most apt to occur in middle-age and in the senile period, and that hereditary influence must be considered. There is no one known con-

stitutional disease with which it is exclusively associated or of which it is a manifestation. It does not appear to be specifically caused by local irritation or traumatism, though this factor, as well as local or constitutional pathologic conditions, may at times have an exciting or contributing influence.

PATHOLOGIC HISTOLOGY

Most authors are in accord with the view, based on histologic evidence, that Dupuytren's contraction of the palmar fascia is caused by an inflammatory or neoplastic process. In 1882, Chevrot reported a thickening of the layer of fascia lying underneath the dermis, which consisted of dense fibrous or sclerotic tissue not containing any connective tissue cells or elastic fibers. The fatty tissue normally separating the fascia from the corium was absent, so that the dermis merged directly into the hypertrophied fascia. The epidermis was thickened, its superficial cells being less horny, less flattened and less compact than normally on account of the immobilization and protection of the surface against friction. The dermis was slightly thickened, and the linings of the sweat glands were apparently thicker than normal. In 1887, Langhans came to the conclusion that the condition was a "chronisch-plastische Entzündung," that is, the trouble was due to a neoplastic or inflammatory change. The change occurred partly in the palmar aponeurosis and partly in the adjacent tissues, including the coats of the arteries and also the capillaries, about which a subendothelial granular adventitia was formed.

Anderson, in 1897, after making careful histologic studies of excised specimens, described the same pathologic process as Langhans and considered the condition "inflammatory hyperplasia or neoplastic growth." But Anderson differed from other investigators, as he thought that the disease is due to micro-organisms that gain access to the subcutaneous tissue through accidental lesions of the epidermis. Culture tests and microscopic search in our own cases always gave negative results, so far as finding a specific organism was concerned. Aside from the fact that it has been impossible to find the organism, this theory also seems improbable in view of the protracted and benign course of the disease and the absence of inflammatory phenomena, and because it throws no light on the bilateral occurrence of the lesion or on the influence of heredity.

Antonioli is also opposed to the germ theory. In the detail of the histology of excised portions of the affected fascia, he stated that there were no leukocytic foci or signs of recent or former inflammation. His investigations seem to indicate a process of gradual transition from a tissue rich in cellular elements to one constituted almost entirely of connective tissue containing increasingly numerous neoformations of col-

lagenous fibers and finally assuming a tendinous aspect. In 1914, Horak also maintained that in no case were there signs of interstitial inflammation, and he grouped Dupuytren's contraction with the borderline conditions between new growths and inflammation.

Both Nichols, in 1899, and Janssen, in 1902, held the same views with regard to the histology of Dupuytren's contraction. They observed that in the early or developing period of the disease, the cellular and vascular elements occur in great abundance, while at a later stage, when the lesion is fully developed and stationary, the cells and vessels diminish, leaving the abnormal tissue a dense fibrous mass. The hypertrophied fibrous bands are developed by the activities of the abundant

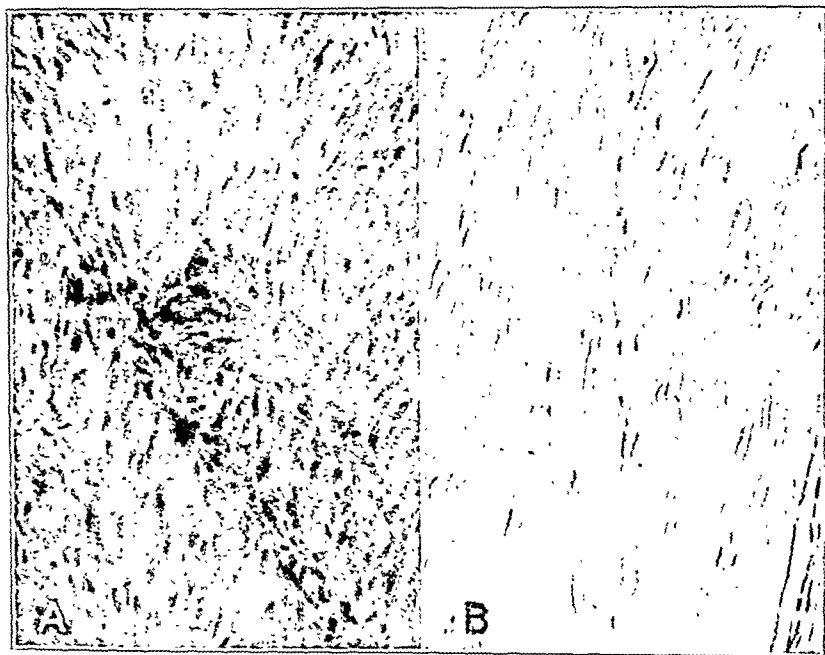


Fig. 5.—Photomicrograph illustrating the difference in the number of connective tissue cells and small blood vessels found in the involved fascia in a recent and an old case of Dupuytren's contraction. *A*, a section of involved palmar fascia in an early case (less than one year) of Dupuytren's contraction. Note the increased number of connective tissue cells and small blood vessels. *B*, a section of the involved palmar fascia in an old case (seven years) of Dupuytren's contraction. Note the small number of connective tissue cells and the scarcity of blood vessels.

connective tissue cells, which are proliferated in special profusion along the course of the small blood vessels. The lesion, therefore, is essentially a focal hypertrophy of connective tissue originating in the walls of the smallest vessels and ending in contraction. There seems to be a predisposition on the part of the connective tissue of the bands toward hypertrophy, which is followed in some places by contraction, probably as a result of changes in circulation. The primary cause of the change

is not known. In Janssen's own words, one has to deal with "flechtweiser Hypertrophie des Bindegewebes, welche von den Wandungen kleinster Gefäße ihren Ausgang nimmt und deren Schicksal die Schrumpfung ist" (braidlike hypertrophy of the connective tissue, which originates in the walls of the smallest vessels and which ends in contraction).

In examining microscopic sections in our own cases, we also came to the conclusion that in cases of recent development the contracted bands consist of a great abundance of connective tissue cells and numerous small blood vessels, surrounded and accompanied by a profusion of cells massed among the fibrous fasciculi. In long-standing cases the contracted bands were less vascular; the vessels present were unaccompanied by an abundance of cells in the adventitia; the connective cells among the fibrous elements were less numerous and in one case were much diminished.

The most recent studies, as summarized by McWilliams, seem to show that the pathologic basis of the contraction of the palmar fascia is a chronic hyperplastic inflammation with subsequent formation of scar tissue in the fascia and the adjacent connective and fatty subcutaneous tissues. This inflammation does not involve these tissues in toto at first, but only certain portions of them: hence the small tumors felt in the palm, the precursors of the disease. As the process develops, it leads within the aponeurosis to a growth and thickening of the loose connective tissue conveying the vessels that lie between the individual fascial bundles. At the same time, there is a thickening and contraction of the delicate connective tissue fibers that bind the fascia to the cutis, resulting in small funnel-like invaginations of the skin, which, together with the small fibrous tumors, lying deeply embedded, represent the first signs of the condition.

Gradually, firm bands appear, radiating from these small, hard tumors in the middle of the palm to the fingers, corresponding to the course of the fascial bundles. The gradual contraction of these bands draws the fingers slowly but surely downward into the palm. Other new connective bands are formed which bind the fascia to the tendon sheaths beneath. The skin itself does not take part in the inflammatory process, but is thrown up into folds running transversely across the palm. In the majority of cases, the changes take place first in the fascia that lies opposite the base of the ring finger, which is usually flexed first and in which the contraction reaches the highest grade. McWilliams, quoting Baum, gives as the reason for this the support that the thenar and hypothenar eminences afford to the other fingers, while the ring finger lies freer and possesses the greatest movement excursion. Besides, the fascia at this point is least protected from trauma. When the process has existed for some time the tendons become shortened and the joint

surfaces are changed in form on account of the change in pressure, becoming atrophic where the greatest pressure occurs, while on the dorsal aspect under the joint surface of the metacarpus, an exostosis sometimes arises. Finally, the joints may become ankylosed.

CLINICAL COURSE

The onset and the development of Dupuytren's contraction is slow and insidious. Usually the patient is middle-aged or elderly and first notices a small nodule or slight induration of the skin on the palmar surface of the hand at the base of the little or ring fingers. Later a minute punctate or funnel-like depression occurs in the palm at the base of these fingers. These signs occur before the contraction of the fingers begins and indicate which fingers will be affected first.

As a rule, no subjective symptoms are noted, except that in an occasional case there is slight pain or tingling in the palm extending up into the fingers. In only three of our cases were such symptoms noticed, and these symptoms consisted of slight burning pain and cramping in the palm and fingers. The vast majority of patients stated that the disease had developed without symptoms of pain or discomfort. In fact, in a number of cases, the contraction was well marked before particular notice was taken of it.

Months and even years may pass before the patient begins to notice a contraction of the affected finger, usually the fourth or fifth, and the development of a band of contracted palmar fascia extending from the concavity of the palm as far as the first or second interphalangeal joints. After a time, the length of which varies, the disease may spread to other fingers, and other contracted bands progressively develop, one for each finger, raised, taut, and closely adherent to the skin. The skin of the palm becomes more and more indurated and creased, and other nodules and funnel-like depressions appear. There is also marked atrophy of the subcutaneous fat.

There is usually complete power of flexion and of joint movements and also of extension in the metacarpophalangeal and proximal interphalangeal joints, except as limited by the contracted fascial bands and secondary contraction of the joint capsule. Motion in the distal interphalangeal joint is usually not limited. The last phalanx may even be hyperextended, owing to the attachment of the digital prolongation of the palmar fascia on its dorsal surface.

When more than one finger is affected, the degree of contraction of one finger has no bearing on the degree of contraction of the other fingers involved. Usually the little or ring fingers are severely contracted, while the others are not affected or only slightly so. In the majority of cases, the condition begins in one hand first, and the contraction rarely develops in both hands simultaneously. When both

hands are involved, they are usually affected to an unequal degree; further, in most cases, the lesions are not symmetrical, but have different locations in the two hands.

The involvement of the palm and fingers may develop in three ways:

1. The disease may be limited to the palmar portion of the fascia.
2. The contraction may be limited to the digital prolongations of the fascia.
3. Both the palm and the fingers may be involved.

In a series of 40 cases reported by Nichols, 8 were in group 1, 1 in group 2 and 31 in group 3. In Byford's series of 38 cases, 10 were palmar, 2 digital and 26, both digital and palmar. In our own series of 40 cases, 66 hands were affected; 11 fell in group 1, 3 in group 2 and 52 in group 3. It will be seen, therefore, that the most common site of occurrence of the disease is in the palmar and digital group and the next most common, in the palm alone; the disease is rarely limited to the digits alone.

DIAGNOSIS

The differential diagnosis of Dupuytren's contraction from other diseases of the hand is usually easy, if one is familiar with the condition. The deformity is so characteristic that in well developed cases it is hard to imagine mistakes in diagnosis, though they are constantly being made.

As a matter of fact, Dupuytren's contraction is often mistaken for flexion of the fingers due to contraction of the tendons following lacerated wounds associated with infections of the tendon sheaths, and also for contractions due to burns. It differs from the contraction of the fingers that follows tenosynovitis by the history and the powerful, free action of the tendons within their limited range. The fingers that are contracted owing to tenosynovitis have lost much of their voluntary power of free flexion. In such cases, there is, as a rule, no palmar induration, and when one attempts to straighten the fingers, the tendons may be felt to become tense above the wrist. In addition, the terminal phalanges are usually flexed, while in the Dupuytren contraction, they are usually hyperextended. In cicatricial contractions, there is the history of injury or infection, obvious scar tissue and absence of the typical features of Dupuytren's contraction.

In the deformities due to arthritis deformans and gout, there are the pain, tenderness and swelling of the joints and the roentgen evidence of bone and joint changes. However, arthropathies may coexist with Dupuytren's contraction, which introduces an element of doubt as to the precise share either condition may have in the production of the deformity present.

Hammer finger (permanent flexion of the distal phalanx) exhibits no palmar or cutaneous changes and is sufficiently characteristic to be readily distinguishable.

All congenital and paralytic contractions of the fingers should be readily differentiated from the contraction of the fingers due to Dupuytren's disease by reason of the dimpling and thickening of the palmar skin and the gradual development of palmar nodules and later of thick cords in the line of the pretendinous bands, involving the skin and fascia which is so definitely characteristic of the latter deformity. In congenital and spastic conditions, the metacarpophalangeal joints are extended and the interphalangeal joints flexed, in direct contrast to the deformity in Dupuytren's contraction in which the flexion usually occurs first at the metacarpophalangeal joints and in which the distal interphalangeal joints may be extended or unaffected. In Dupuytren's contraction the affected fingers cannot be extended even after flexion of the hand at the wrist, since the flexion of the fingers is due to the contracted palmar fascia. In spastic and congenital conditions, however, flexion of the wrist permits extension of the affected fingers, since this maneuver produces relaxation of the long flexor tendons that are primarily involved in such contractions. It is probable that some of the cases diagnosed as Dupuytren's contraction, especially the alleged congenital cases and those stated to have developed in early life, were in reality instances of congenital contractions.

SUMMARY OF OUR SERIES OF FORTY CASES

Age.—Dupuytren's contraction may begin in early adult life, but when these patients are seen for the first time the average age is about 50 years; in our series it was 51. Our youngest patient, a medical student, came for treatment when he was 23 years old; our oldest was 69. Todd presented a girl aged 15 years before the Royal Society of Medicine in 1927 with a typical Dupuytren's contraction. In our series, the onset of the disease was fairly accurately known in 35 cases, and the average age of onset was 42 years. The earliest onset of the disease reported in our series was that of a clerk who first noticed the involvement of his palm and fingers at 18 years of age.

Sex.—In our series, 35 patients were males and 5 females. In 1879, William Adams published a paper in which he said: "I have never seen Dupuytren's contraction in a woman." In 1881, Reeves differed with him because he had seen cases that proved not only that the condition occurs in women, but that it may be regarded as not uncommon in them. In 1882, Adams again stated that he had encountered a case in a woman, but he said that he must repeat that the disease is extremely rare in females. He felt that many authors made the mistake of calling every case of contracted phalanx Dupuytren's contraction. Therefore, care must be taken to detect undoubted evidence of fascial contraction before a case can be grouped in the class described by Dupuytren. This ignorance of the true pathologic process in cases of Dupuytren's con-

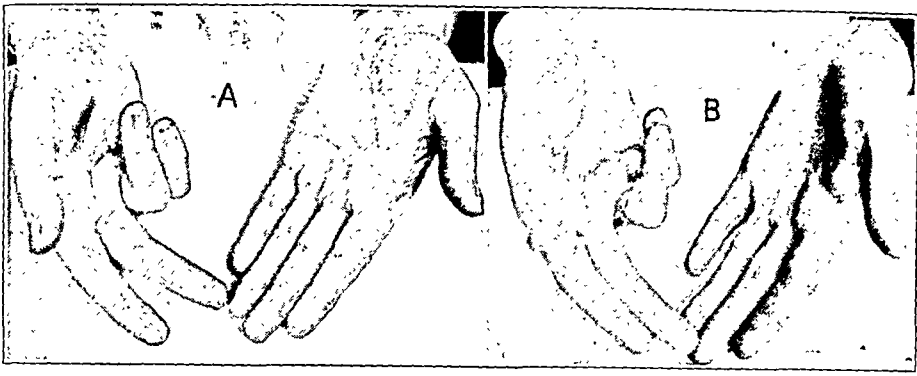


Fig. 6.—The occurrence of Dupuytren's contraction in two brothers. The family history shows that an uncle and a granduncle on the mother's side had similar contractions. *A*, the hands of a priest, aged 53; the thickening of the palm started one year before this article was written, but the progress was rapid, and the contraction of the ring and little fingers interfered with the patient's work. The left hand is uninvolved. *B*, the hands of a clerk, aged 45, with no history of injury. The patient noticed a lump in the right palm four years before this article was written, and there had been gradual thickening, with contraction of the ring and little finger. The left hand was uninvolved. Examination of these photographs shows almost identical contraction of the little and ring fingers of the right hand of both patients. Neither of these patients was included in our series of 40 cases.



Fig. 7.—Photograph illustrating the contraction of the palmaris longus muscle made visible by the prominent tendon at the wrist in a case of unilateral Dupuytren's contraction. The patient, a white laborer, aged 63, had stuck a splinter into the right palm ten years previously. There had been no pain in the hand. Several years prior to presentation, the palm became thickened, lumpy and dimpled at the base of the little and ring fingers. The little finger gradually began to contract, and this was followed by contraction of the ring finger. During the last year the contraction had progressed to a point where it interfered with his work. The hypertension of the palmaris longus muscle can be noted by the marked prominence of the tendon in the wrist.

traction appears all the more incomprehensible when one thinks of the clear light thrown on the nature of palmar and digital contraction by the teachings of Dupuytren in 1831, Goyrand's dissection in 1834, that of Partridge in 1884 and the full accounts of cases by Adams of London in 1875, 1876 and 1878. Noble Smith, in 1884, discussed the supposed immunity of females, and in an examination of 440 elderly women claimed that he found 15 cases of indurated, thickened and contracted fascia and 11 cases of well marked Dupuytren's contraction of the fingers.

Race.—In our series, all but one of the patients were white. (In Baltimore, Dupuytren's contraction is unusual in the Negro race.)

Occupation.—The following occupations were listed in our series: housewife, machinist, carpenter, laborer, butcher, painter, cigar maker,

TABLE 1.—Age of Onset in Various Series of Cases

Author	Cases	Under 30	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79
Nichols.....	45	1 or 2.2%	7 or 16%	6 or 13.3%	16 or 35.5%	12 or 26.4%	3 or 6.6%
Keen.....	90	25 or 27.7%	18 or 20%	47 or 47.7%			
Anderson.....	39	1 or 2.5%	20 or 51%		18 or 46.5%	
Kanavel, Koch and Mason....	29	4 or 14%	6 or 20%	11 or 37%	5 or 17%	3 or 12%	
Costillhes.....	60	9 or 15%	6 or 10%	9 or 15%	21 or 35%	15 or 25%	
Scholle.....	54	8 or 15%	9 or 16.5%	12 or 22%	15 or 28%	10 or 18.5%	
Davis and Finesilver.....	35 out of 40	5 or 14%	9 or 25.5%	12 or 34%	6 or 17.5%	3 or 9%	

teacher, physician, surgeon, engineer, salesman, sailor, policeman, farmer, medical student, clerk, driver, business man, elevator operator and street car conductor.

The relative frequency of the occurrence of Dupuytren's contraction in those who work with their hands and nonworkers in various series of cases is shown in table 3. It will be seen that persons who are constantly engaged in manual labor are less frequently affected than those who do not work, despite the general opinion to the contrary. In our own series, the number was the same in both groups.

Hand Affected.—In our series of 40 cases, the right hand was affected in 8, or 20 per cent; the left hand, in 6, or 15 per cent, and both hands in 26, or 65 per cent. When we first began to study these patients, those with a bilateral condition numbered 20, or 50 per cent, but as we watched them, 6 of those with unilateral cases began to show signs of involvement of the palmar fascia in the other hand and subsequently had a bilateral involvement. Our percentages correspond fairly closely with the average percentages of the total number of cases (701)



Fig. 8.—A very early stage of Dupuytren's contraction in a white man, aged 23, a medical student, born in the United States, who had no family history of a similar condition and who had not had rheumatism, and in whom a focus of infection could not be found. There was no history of injury. A slight localized thickening of the skin of the palm of the right hand had begun three years before this picture was taken. The progress was very slow. Note the typical thickening and dimpling of the skin in the palmar fold. At this early stage, there was no contraction of the ring finger, but rigidity and thickening of the palmar fascia could be felt on palpation. The left hand was uninvolved. On account of the age of the patient and the undoubted progressive nature of the involvement, the palmar fascia was removed as thoroughly as possible, and the result was entirely satisfactory. This patient was the youngest in our series.

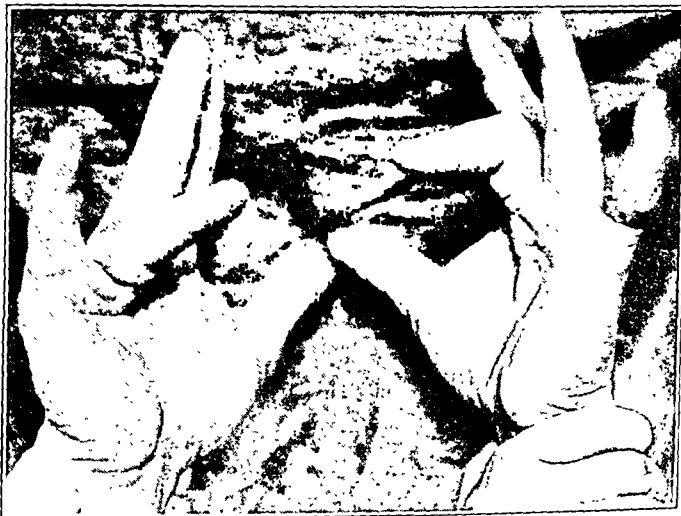


Fig. 9.—Marked bilateral Dupuytren's contraction of different fingers on each hand. A white man, aged 55, born in the United States, a police officer, had had the contracture for twelve years. He first noticed lumps and stiffness in the palms. There has been steady slow progress of the disease since its onset. The patient believed that the condition might have originated when he was working as a stevedore before entering the police force. Note the marked involvement of the ring finger of the right hand, that of the middle finger of the left and also the thickening and puckering of the skin of the palm and phalanges. Note the deep crease in both palms near the wrist where the tendon of the palmaris longus begins to spread. This patient was considerably helped by multiple subcutaneous divisions of the contracted bands, as he was unable to enter the hospital for more radical treatment.

in table 4. Black and Scholle, respectively, noted 48 per cent and 33 per cent in the bilateral group, as compared to an average of 65 per cent reported by most of the other observers. Black and Scholle may have included in their series a great many cases that fell in the younger age groups, while those of us who reported about 65 per cent of bilateral

TABLE 2.—*Relative Frequency of Occurrence in Males and Females in Several Series*

	Cases	Male	Female
Keen.....	227	187 or 82%	40 or 18%
Anderson.....	29	25 or 86%	14 or 50%
Black.....	240	221 or 92%	19 or 8%
Byford.....	38	35 or 91%	3 or 9%
Kanavel, Koch and Mason.....	29	27 or 93%	2 or 7%
Davis and Finesilver.....	40	35 or 89%	5 or 11%
	613	530 or 86.5%	83 or 13.5%

TABLE 3.—*Relative Frequency of Dupuytren's Contraction in Workers and Nonworkers*

Author	Cases	Workers	Nonworkers
Black.....	131	63 or 48%	68 or 52%
Byford.....	38	24 or 63%	14 or 37%
Keen.....	123	49 or 39%	74 or 61%
Kanavel, Koch and Mason.....	29	10 or 35%	19 or 65%
Davis and Finesilver.....	40	20 or 50%	20 or 50%
	361	166 or 46%	195 or 54%

TABLE 4.—*Showing Hand Affected in Several Series of Cases*

Author	Cases	Right	Left	Bilateral
Anderson.....	39	10 or 25.5%	5 or 13%	24 or 61.5%
Black.....	240	89 or 37%	47 or 15%	104 or 48%
Byford.....	38	9 or 24%	4 or 11%	25 or 65%
Costillhes.....	77	14 or 18%	8 or 10%	55 or 72%
Kanavel, Koch and Mason.....	29	4 or 14%	8 or 28%	17 or 58%
Keen.....	184	58 or 31.5%	23 or 12.5%	103 or 56%
Scholle.....	54	28 or 52%	8 or 15%	18 or 33%
Davis and Finesilver.....	40	8 or 20%	6 or 15%	26 or 65%
	701	220 or 31.5%	109 or 15.5%	372 or 53%

cases included in our series many more cases in which the average age was higher than that in the cases reported by these authors.

Fingers Affected.—In our series the fingers involved corresponded closely with those in the 484 collected cases, except that the little finger was involved a few times more than the ring finger. In our cases the fingers were affected 106 times. The little finger was involved 43 times,

or 41 per cent, the ring finger 40 times, or 37 per cent, the middle finger 14 times, or 13 per cent, the index finger 6 times, or 6 per cent, and the thumb 3 times, or 3 per cent.

A study of table 5 reveals that in the 484 cases collected with regard to the frequency of involvement of the fingers, the following order was noted: the ring finger, the little finger, the middle finger, the index finger and the thumb. In a total of 993 fingers, the ring finger was involved in 431, or 43 per cent, the little finger in 339, or 34 per cent, the middle finger in 147, or 15 per cent, the index finger in 48, or 5 per cent, and the thumb in 28, or 3 per cent.

Incidence.—Dupuytren's contraction occurs much more frequently in the later years of life, but it is not a common condition. Only 7 cases were discovered by us in 641 old people examined in the Baltimore City Hospital at Bayview. In 218 white men examined, there were 4

TABLE 5.—*Showing the Fingers Involved in Several Series*

Author	Cases	Thumb	Index	Middle	Ring	Little
Anderson.....	39	4	3	22	39	28
Byford.....	38	4	1	10	35	18
Kanavel, Koch and Mason.....	29	4	3	9	31	27
Keen.....	214	11	24	73	199	165
Noble Smith.....	70	1	6	10	42	30
Scholle.....	54	1	5	9	45	28
Davis and Finesilver.....	40	3	6	14	40	43
	484	28	48	147	431	339

cases; in 140 white women, 2 cases; in 165 Negroes, 1 case; and in 118 Negresses, no cases. If it is true that often repeated traumas of the hands of people who do hard work cause Dupuytren's contraction, more cases should have been found in this group. Among 700 elderly inmates of the London Workhouses, Noble Smith found 55 cases in 300 men and 15 cases in 400 women. The percentage of occurrence in this group and, in fact, in all groups that he reported is much higher than that reported by any other author. It is possible that he included in the group, a number of cases of simple palmar callosities, which are not true cases of Dupuytren's contraction. Anderson found 33 cases among 2,600 persons of the poorer classes of London, almost all of whom were past middle age. De Lom, a surgeon in the British army, reported 3 cases in which patients came for treatment among 203,000 men between the ages of 17 and 35. In 1,106 persons, Byford found 37 cases. Noble Smith examined the hands of 1,000 soldiers between the ages of 21 and 85 years, the average being 53 years and found 40 cases of fascia contraction. None of the 35 colored men examined were affected. In a war department bulletin from the office of the Surgeon General of the United States which gives statistics on the physical

examinations of the first million draft recruits from the ages of 21 to 30, one of the tables shows the number of men accepted with defects for general military services and those rejected at mobilization camps, giving for each disease or defect the number found and the number of cases accepted and rejected. Five men were rejected at mobilization camps for Dupuytren's contraction. Noble Smith found a much larger percentage of cases in the English soldiers he examined, probably because the average age of his group was 53, while in the U. S. group of 1,000,000 recruits the average age was 25 years.

Incidence of Dupuytren's Contraction in Persons with Diabetes.—As it has been mentioned elsewhere that diabetes may be an etiologic factor in Dupuytren's contraction, we investigated this point.

Two hundred unselected patients with diabetes mellitus in the diabetic clinic of the Johns Hopkins Hospital were examined for us by Dr. Herbert Wilgis and Dr. A. Neal Owens. All those with palms and fingers in which there was deviation from the normal were reexamined by one of us, and in this group 6 definite cases of Dupuytren's contraction were found. In none of the cases was the involvement very marked, but in each case selected, we found the typical small fibrous nodules with funnel-like invaginations and dimpling of the skin, with more or less involvement of the palmar fascia, so that there was no doubt about the diagnosis. A number of patients with palmar calluses were rejected and also one or two with contracture due to an old infection.

In the 200 cases examined, 56 patients were males and 144, females. One hundred and fifty-two were white and 48, colored. The oldest was 75 years of age and the youngest, 16. The average age was 50 plus years.

Of the 6 definite cases found, 4 occurred in females and 2 in males. The average age of the females was 62 plus years; that of the males, 54 plus; that of the six patients with the contraction, 59 plus years. One of the men was a telegraph operator and the other a motorman. All of the women were housewives.

There was a definite history of rheumatism in 2 cases, both in women. Hypertrophic arthritis was present in 2 patients, a man and a woman. All of the women had had pyorrhea and had used false teeth for five, twelve, twenty and thirty years, respectively. One man had decayed teeth; roentgenograms of his teeth were taken, and no abscesses found. The other man did not have pyorrhea. Three of this group had had typhoid fever, and all had had the usual infectious diseases. In 4 cases the Wassermann test was made and proved to be negative. The blood pressure of the patients were as follows: systolic

180 and diastolic 120 in a man aged 45; systolic 160 and diastolic 90 in a woman aged 62; systolic 180 and diastolic 100 in a woman aged 48; systolic 170 and diastolic 90 in a man aged 65; systolic 130 and diastolic 80 in a woman aged 70, and systolic 158 and diastolic 74 in a woman 68. There is little to be gathered from these figures, except that in 5 of 6 cases they are higher than normal and in 1 case lower than is usually found at the age of 70 years.

The basal metabolism was $+10$ in the 48 year old woman and varied from -3 to -20 in the others. No significant conclusions can be drawn from these figures. All of the patients were white. There was no family history of a similar condition in any of the group. In 3



Fig. 10.—Bilateral Dupuytren's contraction in the diabetic group. In a white woman, aged 62, the thickening of the palm with dimpling began two years previously in the right hand, and then the left became affected. The patient had pyorrhea, and all her teeth were extracted five years before this illustration was taken. There was a history of rheumatism, pneumonia, typhoid fever and diphtheria. There were typical changes of skin and fascia in both palms, but very little contraction of the fingers.

cases in which the patients were a man and two women, the thickening of the palm was in the early stage and had not been noticed by the patients until the examination was made. In the other 3 patients, also a man and two women, the thickening was first noticed five months before examination in 1 case and two years before in the other two. The involvement in the two men was as follows: in the man 45 years old, there was a thickening of the palmar fascia and a palmar fold at

the base of the ring finger of the right hand, which had begun five months previously; there was no deformity or inconvenience; the left hand was uninvolved. In the other man, aged 65, there was thickening of the palmar fascia in the center of palm at base of the middle and ring fingers of the right hand. There was no deformity, and the inconvenience was not noticed until examination. The left hand was not involved. In the four women the involvement was as follows: In the one 62 years old, the thickening began in the right hand two years prior to examination then started in the left and gradually increased in both until at the time of examination there was involvement of both palms, especially at the base of the ring and middle fingers. At this stage there was only slight loss of function. This was the most severe case of contraction in the diabetic series and the only one in which both hands were involved. In another woman, aged 48, there was a thickening of the palmar fascia at the base of the right ring finger, which was first noticed two years previously, and which had progressed very slowly. There was no deformity or loss of function. In another woman, aged 68, the thickening was discovered at examination; it involved the palmar fascia of the left hand in the palmar fold at the base of the little finger. There was no deformity or loss of function. In the fourth woman, aged 70, the palmar fascia of the right hand was thickened in the palmar fold at the base of the middle, ring and little fingers. There was no deformity or loss of function. In only 1 case were both hands involved; in 4 cases, only the right hand was involved, and in 1 case only the left hand. In none of these cases except possibly in that of the woman with bilateral contraction was operative intervention indicated, and she refused operation.

When we compare the number (6 cases) of Dupuytren's contraction found in this group of 200 diabetic patients with the number (7 cases) found in the examination of 641 persons of approximately the same age examined by us at the Baltimore City Hospital, the condition seems to occur more frequently in diabetic persons than in those with other diseases. It is interesting to note also that in our series of 40 cases of Dupuytren's contraction on which this paper is based, there were 3 patients with diabetes. If the 40 patients who came for surgical treatment are added to the 6 with diabetes and the 46 are taken as a group, 9 of them, or approximately 20 per cent, had diabetes. Although the number of diabetic patients examined is small, these findings are significant, and we hope that they will stimulate further reports on this subject from other clinics.

TREATMENT

There is a wide divergence of opinion as to the best way to treat Dupuytren's contraction, and it may be instructive to consider some

of the procedures advocated at various times. In general, the methods of treatment may be divided into the following four groups:

1. Nonoperative treatment
2. Simple division, or subcutaneous division of the contracted fascial bands
3. Excision of the palmar fascia with closure of the skin
4. Excision of the skin and palmar fascia with skin grafting or flap shifting to fill the defect

1. *Nonoperative Treatment.*—It is now a well recognized fact that the treatment for Dupuytren's contraction is essentially surgical, but it is interesting to mention the more prominent nonsurgical methods that have been used.

Thyroid Extract: In a series of 4 cases of Dupuytren's contraction, in which various treatments (with the exception of extensive operation) had been tried unsuccessfully, Wainwright obtained excellent results by the administration of thyroid extract in moderate doses. This was given by mouth; the dosage, which was $\frac{1}{2}$ grain (0.032 Gm.) at first, was gradually increased, with due therapeutic precautions, to suit the individual patient. In one of Wainwright's cases, the treatment with thyroid extract had been begun eleven years before this article was written, but thyroid has not been taken for the past three years. When seen recently, the patient's hand was flexible and no contraction was present, although some density of the fascia could be felt.

Léopold Levi also tried the administration of thyroid extract by mouth in 7 cases, with favorable results in 5. The daily dose consisted of 10 cg. of thyroid powder, and in 1 case as many as 163 doses were given.

Humanol: Stahnke reported splendid results obtained with injections of humanol in the treatment for Dupuytren's contraction. Since the gliding capacity of the tendon in its sheath is completely preserved in Dupuytren's contraction, this substance was injected into the atrophied aponeurosis, with the expectation that it would become soft under the influence of human fats. The injections are exceedingly painful and therefore must be made under a general anesthetic or local anesthetic. With a rather thick needle a puncture is made on either side of the interdigital plicae next to the sheath of the flexor tendon of the affected fingers. The needle is pushed under the skin until it reaches the transverse fold of the palm of the hand, and 5 cc. of warm humanol is injected from either side. Small injections are made into the region of the proximal and medial phalanges if there are atrophic conditions in that region. Swelling ensues, involving also the back of the hand. Two days later, hot hand baths and stretching exercises are instituted. Two or three weeks later, a second injection is made. Sometimes a marked improvement was observed even after the second injection;

sometimes it was necessary to make five or six injections, which should be the maximum number, at intervals of three weeks. Untoward events were never observed, nor was there any failure, provided the treatment was carried out to completion. Hard places in the palm of the hand may remain, but the extension of the fingers is practically restored. One of the patients, who had been unable to extend the ring and little fingers of both hands, had the function of these fingers completely restored, and this effect has been permanent for over six years. In another patient, good results have continued for three years.

Several other patients were discharged with satisfactory results. Three did not present themselves after the first injection, and several others are still under treatment and show evidences of improvement. The treatment calls for patience. The author prepared the humanol himself from lipomas and omental sections obtained at operation. Patients with specific contractions, that is, contractions on a syphilitic or tuberculous basis, are to be excluded from the treatment as such conditions have nothing in common with Dupuytren's contraction.

Radium: Apert reported a case in which radium was used; an ampule with the emanation was applied to the palm during five nights. The contraction of the fascia relaxed, leaving only a cord, which does not interfere with the use of the hand.

Roentgen Rays: Bécère expressed the belief that the roentgen rays acts favorably in this disease and that it is the method of choice.

Specklin and Stoeber also treated a patient who had palmar and plantar contraction and neuralgia with x-rays and radium, and reported a complete cure. Joly, using deep x-rays, treated a man 60 years old who had a typical case of Dupuytren's contraction. The patient was given four treatments, and when last seen about four months later, he was entirely cured.

Hypnosis: Kingsbury reported an interesting case of a barber with gradually increasing contraction of the palmar fascia. The duration of the condition in the right hand was twelve years and in the left, eight years. There were much pain and cramping of the fingers, and the patient had to put them in hot water to obtain relief. The patient was hypnotized by Liebault's method, and when he became cataleptic, he extended all the fingers and rubbed the palms freely. Following another treatment given on the next day, he remained free from pain and had perfect motion in every finger. We are inclined to believe that this case was one of occupational neurosis rather than true Dupuytren's contraction.

2. *Simple Division or Subcutaneous Division of the Fascia Bands.*—Dupuytren himself used simple division of the fascia bands, and in his original paper described the treatment employed in his first case as follows:

In 1811, M. L., a wholesale wine merchant, in attempting to lift a cask felt a crackling and slight pain in the palm. The ring finger from that time on gradually began to contract toward the palm, and in 1831, twenty years later, the ring and the little fingers were completely flexed on the palm. The skin of this part was folded and drawn toward the base of the contracted fingers.

On June 12, 1831, Dupuytren made a small incision opposite the metacarpophalangeal articulation of the ring finger; the bistoury divided the skin and then the palmar aponeurosis, with distinct crackling. The finger was released and could be extended almost as easily as in the natural state. A similar incision was made opposite the same joint of the little finger; however, only slight relaxation resulted. Finally, a transverse incision was made opposite the center of the first phalanx; the little finger could then be extended easily. The result indicated that the last incision had divided the aponeurotic digitation. The two fingers were then extended by the aid of an apparatus adapted and fixed to the back of the hand. The incisions were allowed to heal by granulation.

Adams, in England, had a large experience in this field and wrote more about subcutaneous surgery than any other surgeon of his time. For the contraction of the fingers (Dupuytren's), he advised multiple subcutaneous division of the palmar fascia, and for this purpose he used a very small tenotomy knife, inserting it under the skin and cutting from above downward. He said that this method is applicable in the severest cases. The finger should immediately be extended and bandaged to the splint, which should not be removed until the fourth day. A splint should be worn night and day for three weeks, and after that only at night for three or four weeks longer.

Drehmann expressed the belief that a great deal can be accomplished by multiple fasciotomy after the method of Adams. He uses a straight, narrow, pointed tenotome, which he introduces between the skin and fascia in three or four places, and cuts downward toward the hand. The after-treatment consists of the use of a small steel splint to be worn at night.

Momburg also advocated the subcutaneous division of the contracted fascia bands followed by a splint worn for eight days and then active motion.

Roth reported two cases in which the multiple fasciotomy method was used. In 1920, he presented before the Royal Society of Medicine in England a patient, aged 28, who had wounded the palmar aspect of the right ring finger; soon afterward he felt that something was pulling down the little finger tightly, and gradually it became bent toward the palm. There was a prominent ridge of palmar fascia in the palm leading up to the base of the ring finger; the skin was adherent to this ridge and puckered by dimples. An operation was performed according to Adams' subcutaneous tenotomy, with complete cure and full power of extension and flexion. In 1927, Roth reported another case in which multiple fasciotomy was used. A man, aged 60, had

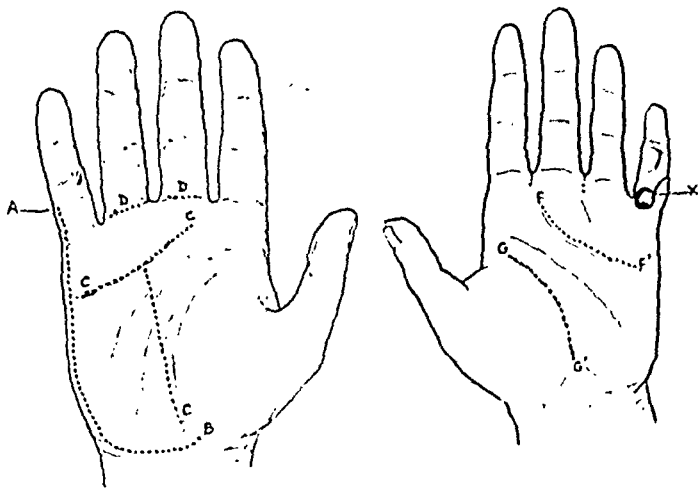


Fig. 11.—The diagram on the left shows some of the incisions that may be used in removing the palmar fascia in Dupuytren's contraction. The curved dotted line *AB* is the incision used by Lotheisen and is not to be recommended. The T-shaped incision *CCC* is frequently used and gives a good exposure. The short transverse line, *D*, across the base of the fingers in the natural fold is between the lateral vessels of the finger and is sometimes useful as a supplementary incision in reaching the fasciculi leading to the phalanges. Care must be taken not to interfere with the lateral vessels. In the diagram on the right the dotted lines *FF'* and *GG'* indicate incisions in the palmar folds. A wide exposure can be made through these incisions when the area between them is undercut, and when these incisions are sutured they heal more satisfactorily than those made across the palmar folds. The incisions indicated by the short vertical dotted lines between the fingers are occasionally useful as supplementary incisions in approaching the transverse fasciculi when they cannot easily be reached from the palmar incision. This incision lies between the vessels going to the adjacent fingers, and care must be taken to avoid these vessels. Line *X* indicates the outline of the flap raised from the outer side of the little finger, which can be shifted in to fill the gap left by the relaxation incision made to release the contracted skin, suggested by Anderson.

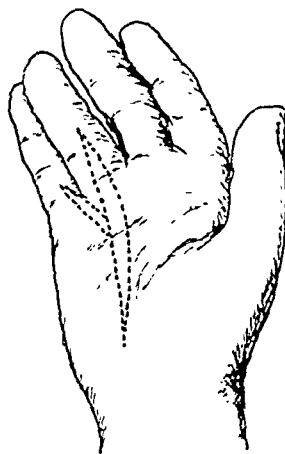


Fig. 12.—The type of incisions used by Oehlecker. The dotted lines indicate the incisions, which are outlined over the contracted fascia bands. The skin within these incisions, with the underlying fascia, is excised, and a wide exposure is obtained. An ellipse similar to that extending to the little finger can also be removed from contracted tissue extending to the middle finger. After the adjacent fascia has been removed and the fingers straightened, the edges of the skin may be sutured. This type of incision cuts across all the palmar folds, and we prefer when possible to make our incisions through the natural folds of the palm.

a contracture of thirty years' duration; the ring and little fingers of the left hand were flexed on the palm. Five weeks after the operation, the patient could fully flex and extend all the fingers.

Sir William Fergusson was himself operated on for Dupuytren's contraction by Adams, who used the subcutaneous multiple fasciotomy method. He said in part:

The operation was only partially successful, but incomplete as it was, the amount of comfort and freedom my hand has received is greater than I ever expected.

Russ advocated an operative procedure that seems to lie between groups 2 and 3, and that is not as conservative as multiple fasciotomy and not as radical as the excision of the palmar fascia by open incision of the skin. He reviewed the radical operations and observed that it is evident that the surgical pendulum has swung to its extreme in the direction of open operation. He said that one should not forget the good results with the subcutaneous operation reported by many observers and the fact that Adams, who probably had the largest experience in the field, has made the statement that the method is applicable in the severest cases. Russ began his operation on the contracted fingers instead of the palm.

After the parts are thoroughly cleansed, small incisions, running in the axes of the fingers, are made with a sharp, pointed, straight bistoury on the palmar surface and directly over the affected joints. An incision measuring 1 cm. is all that is required. The skin and subcutaneous fat are carefully dissected back and the long fibrous band excised, and then an endeavor is made to straighten the finger. This is usually not possible, and it will be found necessary to pass the knife down deeply around the joint. A gritty sensation warns the operator when he has arrived at the lateral fibers, which sometimes run nearly as far back as the extensor tendons. These fibers are in turn divided. The fingers are not yet quite free, and it remains for the operator to remove the heavy fibrous bands that run in the palm toward the fingers. This is accomplished through comparatively short incisions. The skin is then undermined on all sides, and it is surprising how much can be done through a small opening if the surgeon is possessed with the necessary patience and if he exerts a proper amount of care. As much of the glistening palmar fascia as can be seen in the vicinity of the bands should be removed as thoroughly as possible. Bleeding is generally considerable and is controlled by an Esmarch bandage about the wrist.

The fingers are placed in extension on a dorsal wooden splint. Passive movements should be begun as early as possible, sometimes as early as the sixth day, and the splint is omitted after the tenth day. An effort should be made to perform the work thoroughly through a small incision, for operative wounds of the hands do not often heal kindly, and a large resulting cicatrix will not only be unsightly, but may limit motion as well.

Russ performed the aforementioned operation under local anesthesia produced by procaine hydrochloride, but he prefers a general anesthetic. In mild cases he obtained anesthesia for a period of half an hour by

infiltrating the median and ulnar nerves with a 2 per cent solution of cocaine. The purpose of outlining the aforementioned procedure is to emphasize the fact that it is possible to perform the operation through smaller incisions than have heretofore generally been used.

Multiple transverse division of the fascia through a longitudinal incision was advocated by Hardie, Kocher, Kestley and others. A longitudinal incision is made over the contracted band, and the skin is separated from the fascia as completely as is possible. The fascia band is divided in as many places as may be necessary to release the fingers. The skin is closed, and the hand is splinted. Recontracture may occur, but the procedure is an improvement over Adams' operation of subcutaneous division of the fascia.



Fig. 13.—Exposure of the palmar fascia obtained through a T-shaped incision in a case of Dupuytren's contraction. The edges of the skin, which have been partially separated from the fascia, are retracted by sutures. The fascia itself can be seen in the floor of the wound; it was removed as completely as possible, including the fasciculi to the fingers. The healing following this operation was by first intention. There has been no sign of recurrence after several years.

3. *Excision of the Palmar Fascia with Closure of the Skin.*—The best surgical opinion now holds that in the majority of cases excision of the palmar fascia is the method of choice. The older methods of operation have been abandoned, and the method first reported by Kocher in 1887 is the one now most commonly used. It is based on the principle that if the palmar aponeurosis and its processes are diseased, they should be removed. This is done through simple longitudinal incisions in the skin, which is dissected free from the nodules and the cords beneath it. After these are excised, the incisions in the skin are closed by suture. Kocher reported four cases in which operation was performed in this way with good functional results.

In 1902, Doberauer reported seven cases from the Wolfler Clinic in which operation was performed according to the Kocher method. He expressed the belief that the method of excision of the palmar fascia with suture of the skin, if performed with careful observation of the rules set forth by him and if careful after-treatment is given, will make it possible to dispense with the more radical types of operation. From his experience, the author concluded that general anesthesia is the method of choice, as there is danger of gangrene with any type of infiltration anesthesia, and moreover it is not always sufficient, as the operation sometimes requires a long time. He uses the Esmarch bandage and practices careful hemostasis, as a subcutaneous hematoma may also cause gangrene of the skin. He uses a linear incision rather than a flap, and he expressed the opinion that in one of his cases, the flap was responsible for gangrene. The incision should always be carried to the basal phalanx of the finger in order to remove the digital

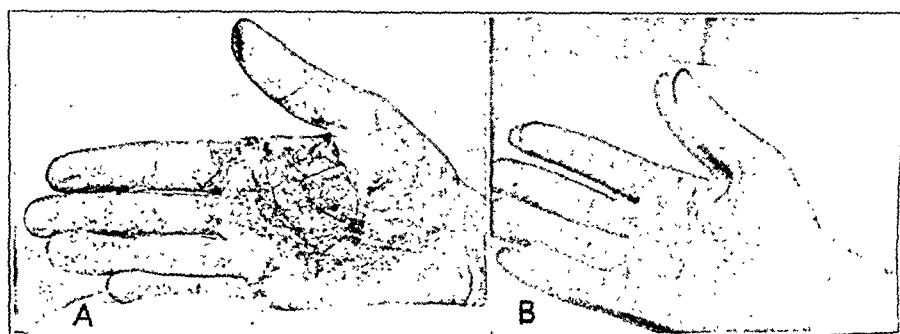


Fig. 14.—The use of incisions made through the palmar folds. *A*, taken ten days after operation for the excision of the palmar fascia in a case of Dupuytren's contraction. Note the straightness of the fingers and the horsehair sutures still in place. *B*, one week later. Note the satisfactory healing and the small amount of damage done to the skin of the palm.

process of the aponeurosis. This method does not prevent recurrences in the fingers not involved at the time of operation, as total removal of the palmar aponeurosis is not possible. But the fingers operated on can be restored to complete function, if the patients do not withdraw from the after-treatment of massage and passive motion which must continue for many weeks.

Byford, too, stated that the treatment for Dupuytren's contraction is purely surgical, and that the open operation with dissection of the palmar fascia from the skin and the underlying structures is generally performed. He follows this by use of splints for one month constantly then intermittently for another month and then applied at night for from six to eight months. He also made the following important observation: in operating on such hands, the surgeon must be sure that

the contraction is stationary. To insure against a second hypertrophy and contraction of the fascia, a thorough general examination should be made, and all sources of infection should be removed. A careful measurement of the contraction compared with a second measurement made six months later will indicate whether or not the condition has become stationary. If it has been stationary for six months after the removal of all foci of infection, the probability of a second contraction is slight.

Ely also agreed that all foci of infection should be removed in addition to excision of the palmar fascia to prevent progression or recurrence of the contraction. He found that all of his patients had infected teeth. One patient, a medical student, had diseased tonsils. Ely advocated as the first step in the treatment for Dupuytren's contraction the removal of all dead teeth.

Antonioli also advocated the operative procedure and detailed two cases demonstrating good results obtained by "aponeuroectomy," excision of the palmar fascia.

He proceeds under general anesthesia and uses the Esmarch bandage. In the first case, that of a man, aged 60, with a bilateral Dupuytren's contraction, he made a triangular flap which gave access to the hollow of the hand. He isolated the palmar aponeurosis, starting from its proximal portion, and dissecting en bloc all the diseased and thickened portion and the adjacent healthy parts, up to their digital ramifications, and then replaced and sutured the skin flaps with interrupted sutures. After fifteen days, massage and active and passive movements of the fingers were begun. Motility of the fingers, including active extension, returned completely within a few weeks. Seventeen months after operation, the result remained excellent. The other patient, a woman, aged 51, had a typical contraction of the palmar fascia and ulnar three fingers of the right hand. She was operated on in the same way, and an aponeuroectomy was performed. Six months after operation, the fingers were perfectly extended, and the sensibility of the skin of the palm and fingers was nearly normal.

Gill also excises the contracted palmar fascia by open operation and adds a free fat transplant from the thigh to the hollow of the hand before closing the skin flaps. With the patient under general anesthesia and without a tourniquet, a transverse incision is made along the distal palmar crease, and through this incision alone the entire palmar fascia is removed. If contracted fascia is present on the palmar aspect of the proximal phalanges, it may be excised through transverse incisions along the crease at the base of each finger involved. A small free fat transplant from the thigh is inserted smoothly beneath the palmar skin without sutures. The incision is then closed with a few interrupted sutures of chromic catgut (number 0).

In 1915, Spitzky employed free fat transplants in cases of contraction of the fingers and hands other than Dupuytren's contraction. In 1917, however, Peiser first reported the use of a free fat transplant from the abdominal wall in an operation for Dupuytren's contraction which he performed on June 19, 1916.

Hutchinson is another surgeon who advocated the open operation, with the excision of palmar fascia. His method of dealing with the contracted fingers in cases of Dupuytren's contraction of long standing is both original and ingenious. He stated that continued contraction after the usual operation is probably due to the fact that the glenoid ligament in front of the first interphalangeal joint, as well as the lateral ligaments, becomes shortened and incapable of extension. He insisted that the only way to overcome this is to excise the head of the first phalanx. His procedure is as follows: 1. The bands of palmar fascia,

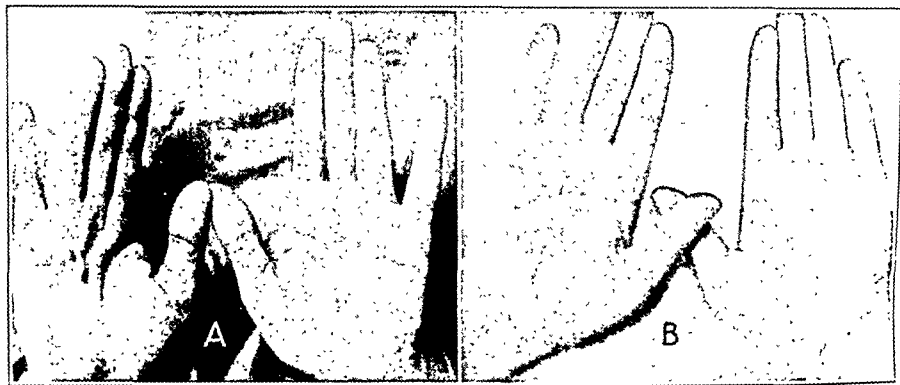


Fig. 15.—A case of Dupuytren's contraction in which trauma may have been a factor. A white man, aged 45, a chemist, born in the United States, several years before this picture was taken had used a short handled pestle, which pressed against his palm, in grinding material for his work, and he felt that the pressure might have been the cause of the condition. He first noticed a stiffness and thickening of the skin of the palm, which gradually increased until the ring and middle finger could not be completely extended. There was a sensation of drawing and "tingling." In *A*, note the lumpy involvement of the center of the palm with bands extending to the ring and middle fingers, also the dimpling of the skin. At this time, the left hand was uninvolved, but when seen two years later contraction of the palmar fascia was beginning on that hand. *B*, result of closure six weeks after excision of the palmar fascia through a T incision. Sometimes when the skin is particularly indurated, the tips of these flaps may slough, but without detriment to the ultimate result. Note the absence of the fascia bands and the full ability to extend the fingers.

including the prolongations over the first phalanx, are excised and then the wound on the palm is sutured. 2. On the dorsal surface, a semi-lunar incision is made over the first interphalangeal joint; the extensor tendons are divided, and the head of the first phalanx is excised. 3. The extensor tendon is slightly shortened. The finger is now somewhat

shorter than normal, but it is straight without tension. 4. A splint is not used in the after-treatment. Gentle active and passive motion should be resorted to within the first few days. No digit should be allowed to stiffen. Hutchinson expressed the belief that long continued splinting frequently results in stiff joints and a recurrence of contraction.

Recently Abbott reported the use of a transplant of fascia lata after the excision of the palmar aponeurosis. He advocated wide excision of all the diseased fascia followed by an immediate transplantation of a piece of fascia lata from the thigh, and reported almost perfect anatomic and functional results in most of his cases. In this fascia transplantation operation the following points are important: 1. As fine a piece of fascia as possible should be obtained. 2. The transplant should be larger than the defect in the palmar fascia to allow for shrinkage. 3. The fascia should merely be tacked in place so as not to strangle any portion of it by tight sutures. 4. There should be absolutely no tension in the transplant and complete hemostasis. Abbott recommended that after this type of operation the patient should be kept from work for at least three months in order to avoid all source of irritation. Light work is advisable for a further period of three months.

In support of the open type of operation with excision of the fascia is the report of an interesting case presented by W. Muir Dison before the Royal Society of Medicine in 1927. He performed an operation in a bilateral case, and after eighteen months the condition recurred on the side in which subcutaneous multiple fasciotomy had been performed, while the side on which open operation was done remained satisfactory.

It may be advisable to perform a combination operation in stages. That is, the fascia may be divided by one of the methods described previously, which allow extension, and then after healing is complete this may be followed by a more radical procedure.

4. *Excision of the Skin and Palmar Fascia with Skin Grafting or Flap Shifting to Fill the Defect.*—Janssen saw a number of patients on whom operation was performed in the von Bergmann clinic from 1886 to 1897 by the Kocher method; in almost all of them the condition had recurred. It could be seen that after the diseased parts of the aponeurosis had been removed, the pathologic process had continued in the parts left behind; this fact suggested that permanent cure could be effected only by the radical removal of the whole aponeurosis and its ramifications. This led Lexer to remove not only the whole aponeurosis, but also large parts of the skin over it or the whole skin of the palm of the hand if it was adherent to the fascia or in any way involved. While this operation is unquestionably radical, Lexer insisted that it must be performed even in the milder cases if the progress of the disease is to be stopped. The defects were then filled with free skin grafts or pedunculated flaps taken from the abdomen or chest. Lexer operated on eight

patients in this way, with excellent results. In one case, a pedunculated flap was made from the skin of the breast and the pedicle cut after ten days. The flap was made large enough so that its edge could be used to cover the defect on the palmar side of the finger. The result was excellent; the edema of the flap soon receded, and the position and mobility of the finger were excellent. In other cases, the defects were covered by free grafts of skin taken from the thigh. After a time the sensation in these grafts became completely normal.

In the Czecho-Slovakian clinic Horak reported twenty-two cases in which operation was performed according to the Lexer method. All skin showing any change was excised, and then the defects were filled with free transplants of skin. The results in these cases were uniformly good.

In a recent article, one of the best articles in English on Dupuytren's contraction, written by Kanavel, Koch and Mason, which appeared in print while this paper was in process of preparation, is the following statement as to treatment, and we are entirely in accord with it:

In the light of our experience, we believe that the essential factors in the treatment are as complete an excision of the palmar fascia as can be accomplished through the operative incision most suitable for the case in question, the excision of hopelessly affected skin, and primary closure of the wound without undue tension. In some cases, this may involve the use of a free full thickness graft of skin to replace the excised covering tissue.

PERSONAL EXPERIENCE WITH METHODS OF TREATMENT

Nonoperative Methods.—When a patient with Dupuytren's contraction presents himself, it is important, whatever method of treatment is ultimately chosen, that a thorough physical examination is made for the purpose of locating foci of infection and concurrent disease. If such a condition is found, steps should be taken to correct it before operative treatment is commenced. Infections must be cleared up, sugar in the urine controlled, etc.

As operative procedures seldom appeal to the patient except in advanced cases in which the deformity greatly interferes with function, all sorts of nonoperative methods have been used to obtain relief from this condition. Among them are the following: the use of splints of various kinds and extension apparatus worn over long periods, massage, passive motion and stretching, hot and cold baths, baking, electrotherapy, the injection of liquefied humanol to soften the contracted fascia, the injection of a fibrin ferment, the administration of thyroid extract by mouth to counteract thyroid deficiency, inunction with various ointments, hot fomentations and even hypnotism. Good results have been reported with all of these procedures, and the reports may be true; however, these methods may be placed in the group of procrastinating measures.

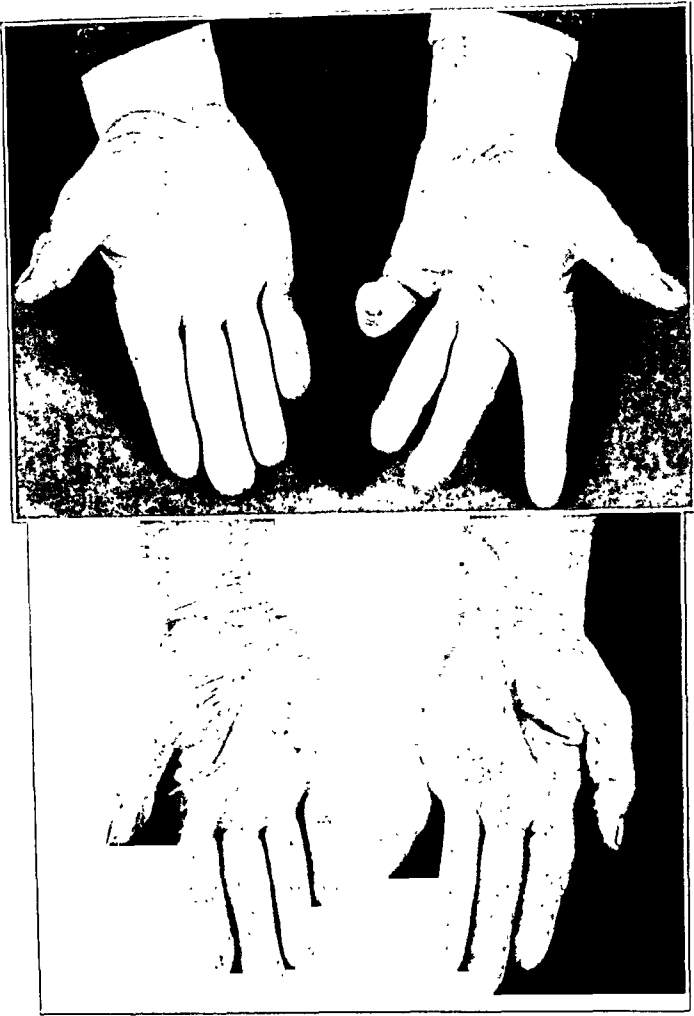


Fig. 16.—The upper picture illustrates the difference in the degree of Dupuytren's contraction in the individual hands. The patient, a white man, aged 45, born in Austria, a laborer, had not had rheumatism or gout. The teeth were in poor condition. The patient was operated on for mastoiditis several times eighteen years previous to presentation. He had noticed a hard area in the palm of the left hand over the metacarpophalangeal joint nine years previously. Thickening and contraction gradually increased until the condition became so marked that it interfered with the handling of tools. Note the typical involvement of the skin of the palm and the contraction of the ring and little fingers, with slight involvement of the middle finger. On the right hand can also be noted the typical beginning dimpling and thickening of the skin between the palmar folds at the base of the ring finger. This condition had not been noted by the patient. The palmar fascia was excised from both hands simultaneously by two operators, and the contraction was relieved. In this case a hematoma formed in the left palm after operation, and it was removed. The lower picture shows the result of excision of the palmar fascia in both hands after six months. The scars can scarcely be seen. The little finger is still slightly flexed on account of shortened skin, and function is excellent in both hands. The patient resumed his occupation. Note that the dimpling of the palmar skin of the right hand remains. This did not disappear when the fascia was excised, and, as we did not desire to shorten the palmar skin, it was not removed and will cause no future harm as there is no deep connection with a strand of fascia.

as we have never seen a patient who had obtained permanent relief from a true, well authenticated case of Dupuytren's contraction following any of these procedures, although as yet we have had no experience with humanol or hypnotism. When good results have been reported, possibly the diagnosis has been at fault and some other condition has been successfully treated. As a matter of fact, a number of the patients who have come under our care have received one or many forms of non-operative treatment before applying for relief by operation, and in all of these patients there has been a steady increase in the severity of the contraction instead of permanent relief.

In other words, in our opinion none of these nonoperative methods of treatment may be depended on to cure the contraction; nevertheless, several of them, such as massage, passive motion, stretching and splints, are extremely useful as adjuncts to the operative treatment.

The use of radium for relief from true Dupuytren's contraction has not been successful in those instances in which we have seen it tried. Several months ago, one of us saw a patient with rather marked Dupuytren's contraction in which the progress of the disease was apparently stopped and considerable relaxation was obtained by the use of the roentgen rays. This patient was treated by Dr. L. B. Morrison of Boston, who in a personal communication indicated his method of treatment as follows: He gave about two thirds of an erythema dose just over the area, using 140 kilovolts, 3 mm. of aluminum being used as a filter. If erythema is avoided, there is practically no possibility that later changes will occur in the skin. The treatments are given once every three weeks, usually for five times. Then after an interval of three months, two or three more treatments may be given, depending on the condition of the contraction.

This method is being tried out for us on several patients (not included in our series) with Dupuytren's contraction who were unable at present to undergo operative treatment. In all of these there has been definite softening of the thickened fascia and a reasonable amount of relaxation, which we think is sufficient to warrant further trial. We feel that in such cases the roentgen rays and radium should be used only by experts with the greatest care, as burns of the palmar skin and underlying structures materially complicate the ultimate success of operative work.

Operative Methods.—If an operative procedure is undertaken, the hand should be thoroughly prepared by the method of choice, and every effort should be made to maintain asepsis until healing is complete.

Anesthesia by median and ulnar nerve block at the wrist may be used, but we prefer a general anesthetic in the majority of instances in which a radical operation is done. In operations for excision of the fascia and for excision of the skin and fascia with replacement with a

graft or flap, it is advisable to use a tourniquet so that the work can be done in a bloodless field. All hemorrhage must be checked before the wound is closed. Every effort should be made to avoid injury to the digital nerves and to prevent interference with the blood supply. The flexor tendons must not be disturbed. Fine needles with horsehair should be used for closing the skin, and we have found the on-end mattress suture the most effective.

Subcutaneous Division of the Contracted Fascia Bands: Division of the skin and of the underlying contracted bands of fascia was advocated and successfully used by Dupuytren, but it was soon found that division of the skin over the bands was unnecessary, as the same results could be obtained by the introduction of a small tenotome through a tiny wound, with subcutaneous division of the bands. When multiple subcutaneous division is to be done, a very narrow pointed tenotome is inserted between the skin and the fascia where they are not tightly adherent, and the cut is made through the contracted band toward the palm. The finger should be on the stretch and the fascia should be divided in as many selected places as necessary, special attention being given to the fasciculi on the fingers. Some advantage may be gained by sweeping the narrow blade around parallel to the skin, thus dividing the fibers going to it. It is seldom necessary to suture the tiny wounds made by the tenotome. The use of a splint for several days immediately after operation and for two or three weeks thereafter at night is helpful. Massage and constant stretching are also advisable. The injection of a fibrin ferment, in addition to division, has been without beneficial result in our hands.

In certain instances, subcutaneous division of the contracting bands is advisable, for example, when the physical condition of the patient will not permit more radical measures and also when the patient requires help but for various reasons is unable to enter the hospital. We have in mind the case of a police captain who had marked progressive contraction beginning in the ring finger on one hand and the middle finger on the other. He had carefully kept this condition from official observation until loss of function became so definite that he was unable to continue his duties without relief. Fearing retirement if the trouble was discovered, he was unwilling to enter the hospital for treatment. In this case, multiple subcutaneous divisions of the affected fascia bands were done on several occasions with the patient under local anesthesia, and with the aid of splints worn at night and vigorous, frequently repeated stretching, he was able to continue his active work until his death several years later. Except in cases of this kind, or, in other words, in cases in which radical measures cannot be carried out, we do not favor the method, because however slight the contraction is, it usually recurs, as the affected fascia is not removed, but is merely divided. However, the

method may sometimes also be used advantageously as a preliminary operation to be followed, if necessary, by the more radical procedure of excision of the palmar fascia.

Subcutaneous division of the fascia bands is certainly much more effective than any of the nonoperative methods, and improvement follows in certain instances.

Excision of the Palmar Fascia: If the skin of the palm and fingers is in fairly good condition and is not involved seriously enough to prevent subsequent closure, the method of choice in the treatment for

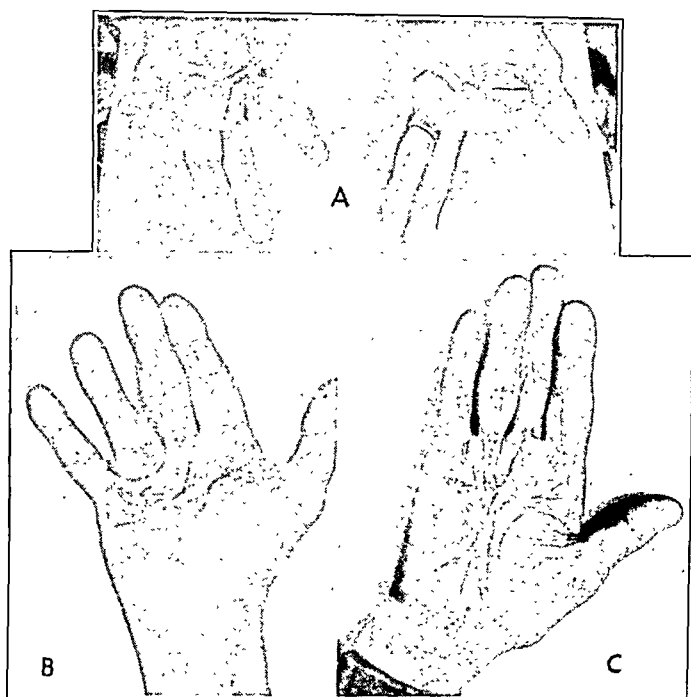


Fig. 17.—Bilateral Dupuytren's contraction in markedly different stages of development. *A*, a white woman, aged 63, a housewife, born in the United States, whose mother had a similar condition in one hand, but not to such a marked degree. The patient was operated on for appendicitis fifteen years before this picture was taken. Her teeth were in excellent condition. She had not had gout, rheumatism or any injury. The thickening of the skin of the right palm began five years previously and progressed slowly, gradually flexing the ring finger and, to a lesser degree, the little finger. During the last six months the flexion increased much more rapidly. Except for tightness and gradual loss of function, there were no special symptoms. The left hand shows beginning involvement of the palmar fascia with lumping and dimpling of the skin in the palmar fold at the base of the ring finger. This had been noticed during the last two months. *B*, closer view of right hand. Note the marked involvement of the skin of the palm; it was so indurated that it was questionable whether it could be flattened out and sutured or whether it should be excised and the defect grafted. *C*, three and a half months after excision of the palmar fascia through a T-shaped incision with closure. The tips of the flaps sloughed in this case. Note the difference in the appearance of the skin of the palm and the improvement of the fingers.

Dupuytren's contraction is as complete excision of the palmar fascia as can be accomplished. If possible the incisions should be made in the natural creases of the hand, but no single incision is to be especially advocated in all cases. The fascia should be exposed through the incision or incisions that will do the least subsequent harm. As the disease is always progressive, we feel strongly that excision of the involved portion of the palmar fascia with a very wide margin is advisable even in the earliest stages.

The skin should be carefully dissected free, every effort being made to avoid button-holing or thinning it enough to cause subsequent slough. Then the diseased fascia as well as all the fasciculi leading from it should be removed. The digital nerves and interference with the blood supply should be avoided. When the involvement is well advanced, and in fact in every case, it is safer to dissect out the entire palmar fascia, both involved and uninvolved, from its narrow proximal portion, including the fasciculi running to the front and the sides of the fingers, and all connecting bands both superficial and deep. Frequently most of the subcutaneous fat has disappeared, and the dissection of the skin from the fascia is difficult. After the fascia has been dissected out, the Esmarch bandage should be removed and the bleeding checked completely. Occasionally we place a thin graft of fat, or of fat and fascia beneath the skin before closing, as this may prevent cutaneous adherence. The skin is then sutured with on-end mattress sutures of horsehair over which is placed gauze impregnated with a 3 per cent bismuth tribromphenate ointment, and finally a sterile sea sponge which is applied to the hand with even pressure. The fingers should be fully extended and the hand and wrist supported by a properly padded splint.

The splint should be allowed to remain for about ten days, and then the stitches are gradually removed and slight motion is begun. The use of the splint should be continued for about two weeks longer, being removed daily for massage and passive motion, after which time it may be omitted, except that it should be worn nights for about two weeks longer. The results of excision of the fascia with closure of the skin are satisfactory as a rule.

Excision of Skin and Fascia: When the contraction is marked and the involved skin is very thin, atrophied, anemic and closely adherent to the thickened lumpy aponeurosis, there is little use in trying to save it by dissecting it free from the palmar fascia, as it cannot be used for closure. In such a case, time is saved and a better ultimate result obtained by complete excision of the palmar fascia, as previously described, with that portion of the overlying affected skin which cannot be utilized. Sometimes the palmar skin on the proximal phalanges must also be removed. A measured graft of whole thickness skin may be sutured into the defect with good result, and in many instances this



Fig. 18.—The upper pictures illustrate the full amount of extension possible and the interference with function in a case of Dupuytren's contraction. In a white man, aged 51, a bond salesman, born in the United States, with no family history of the condition, the contraction began seven years before this picture was taken in the middle finger of the right hand, then the ring finger became involved, and about three years before the little finger began to contract. In one year it reached its present condition, which prevented the patient from playing golf. The skin of the palm and of the palmar surfaces of the third, fourth and fifth fingers was thickened and lumpy. The fascia bands were markedly contracted. The index finger was normal. The left hand was seen two years later, however, the same condition was beginning in the left hand. As the skin was too indurated to suture, it was determined to excise the palmar portion with the fascia and digital prolongations. A roentgenogram showed the joint surfaces uninvolved.

The lower pictures illustrate the use of a pedunculated flap of skin and fat in filling in the defect left by excision of badly indurated and contracted skin and palmar fascia. The lower left picture shows a single pedicle flap raised from the abdominal wall and immediately implanted into the defect made by the excision of the skin and palmar fascia. Note the size of the flap sutured into the palm, of the position of the hand and also the pedicle of the flap which is still attached to the abdominal wall. The patient declined to return to have the flap shaped and flattened, as he was completely relieved of his symptoms, and function was sufficiently restored to allow him to play golf. Note the puffiness of the middle and ring fingers. The skin on these fingers was originally much involved but was not excised with the palmar skin, although the fasciculi of the palmar fascia beneath were removed. There was slight flexion due to shortening of the involved skin. The appearance of this hand could be much improved by further operative work. There seems to be no tendency to recurrence after four years.



Fig. 19.—Photographs illustrating the necessity of amputation in cases of Dupuytren's contraction when the phalangeal joint cartilage has been involved. A white man, aged 31, a machinist, born in the United States, with no history of special trauma and with pulmonary tuberculosis, noticed "lumps" on the little finger of the left hand five years before this picture was taken. Gradual contraction and loss of function occurred. *A* shows amount of extension possible. Note the involvement of the little and ring fingers. *B*, the palmar fascia was excised through a horseshoe-shaped incision running from the side of the little finger downward on the ulnar side of the palm and across the wrist to the thenar eminence; the fingers were straightened as thoroughly as possible. The skin of the palm at the base of the little finger was too indurated to give satisfactory healing, and a thick scar resulted, which might have prevented further extension of the little finger. Besides, the roentgenogram showed the cartilage of the proximal interphalangeal joint of the little finger to be defective. *C*, the contracted thick scar at the base of the little finger was replaced by a flap from the abdominal wall which relieved this contraction. *D*, the roentgenogram shows changes in the cartilage of the proximal interphalangeal joint of the little finger with subluxation. It was found that this joint did not readjust itself although the finger was almost straight and that ankylosis resulted. *E*, subsequently, amputation was done as the stiff finger was in the way.

procedure is the method of choice. In some cases a delayed transfer pedunculated flap of skin and subcutaneous tissue previously prepared on some convenient area is to be preferred, as it is more certain to take and has the advantage of supplying skin and fat at the same time. The latter procedure is much more trying to the patient, but in advanced cases is very helpful. Excellent results are obtained by both of these procedures.

Secondary Operations: In instances in which the original operation has not been complete, or, in other words, in which only part of the palmar aponeurosis has been excised, recurrence of finger contraction is not uncommon. In such instances a radical excision of what remains of the palmar fascia is indicated. Localized puckering and thickening of the skin may occur, for instance, on the thenar and hypothenar eminences

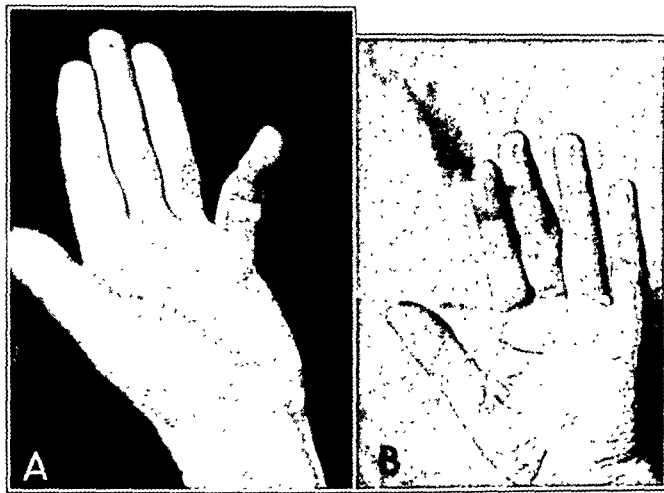


Fig. 20.—The result of excision of the palmar fascia for relief from Dupuytren's contraction. *A*, Dupuytren's contraction involving the little finger of the left hand. In the patient, a white farmer, aged 54, born in the United States, the condition began five years before the photograph was taken with typical involvement of the skin and fascia and contraction of the little finger. The palmar fascia was excised and the skin closed. *B*, the same hand after twelve years. Note the ability to extend the little finger and the absence of recurrence, except over the metacarpophalangeal joint of the thumb, where evidently some fibers of the fascia were not excised. This patient was operated on in the same way for a similar condition of the little finger of the right hand seventeen years before without recurrence.

where some of the fibers of the aponeurosis have been missed, as it is difficult to find and remove every particle of the aponeurosis, especially if it is as yet uninvolved. When puckering occurs, it is undoubtedly due to progressive fibrositis of the fasciculi that still remain, but in these cases marked degree of contraction seldom occurs, and the operative procedure is merely the removal of the local condition.

COMMENT

In certain cases of long standing in which there is marked contraction, we have found destruction of the joint cartilage and ankylosis of the phalangeal joints, in addition to advanced fibrositis of the fascia. In these cases, amputation of the finger may be necessary. In marked cases of flexion of joints, if the joint surfaces are intact, the procedure of removing the head of the phalangeal bone and shortening the extensor tendons as advocated by Hutchinson may be avoided by loosening the glenoid and lateral ligaments from the proximal phalanx and allowing them to slide upward as the finger is extended. We have also used this method successfully in congenital contractures of the fingers. Shortening of the extensor tendon, which has been advised after removal of the head of the phalangeal bone, also seems unnecessary and can be avoided by this procedure, as the slack is soon taken up by natural contraction, and the possibility of tendon adhesions is thus avoided.

In other cases of long standing, though the palmar skin of the contracted phalanges is apparently uninvolved in the fibrositis, it is shortened, and because of this shortening, the finger cannot be fully extended even though all of the contracted aponeurotic bands have been divided or excised. In such a case, relaxation of the shortened skin by a suitable incision, followed by the transplantation of a full thickness graft is the procedure of choice.

The question often arises as to whether the progress of Dupuytren's contraction can be checked in any other way than by radical operation. Except for clearing up focal infections, treating intercurrent diseases and using local measures such as massage and stretching, we have found nothing so far to prevent its steady progress. However, in casting about for some way in which this might be done, we noted with interest an observation made many years ago by Noble Smith, which is discussed in the section on etiology in the group of miscellaneous theories. Briefly, he said that the palmaris longus muscle was tense and prominent in nearly every case of Dupuytren's contraction, and that the long continued contraction of this muscle, however induced, might be the cause of the irritation of the palmar fascia. He suggested that, if done in the early stages, tenotomy of this muscle might stop the development of the disease. We have also observed in several early cases that the palmaris longus muscle was tense and contracted, and hereafter in cases in which the contraction is present we intend to try division of the palmaris longus tendon in the wrist.

Following the tenotomy, massage and other treatment should be continued for six months; if at the end of this time there has been progress in the contraction, the fascia should be completely removed. On the other hand, if there has not been progress of the disease, the

patient should be kept under observation and operation performed whenever there is progression of the contraction. While this procedure may have no effect we feel that it is worth giving a trial as it is simple and can be done under local anesthetic without danger. We shall report subsequently on the result of our observations on this procedure.

In addition to division of the palmaris longus tendon, it might be advisable to try treatment with the roentgen rays in the way suggested by Dr. Morrison and described earlier in the paper, if this treatment can be done by an expert.

It is more difficult to get an accurate approximation and a smooth healing of the skin in the palm and the sole, even when they are normal, than in other parts of the body, probably on account of the thickness of the horny layer. Naturally, this approximation is even more difficult when the skin is involved in cases of Dupuytren's contraction, and the early appearance of the healing in these cases, although it may be by first intention, is not as satisfactory as in skin in which the horny layer is thinner. Eventually, however, the suture lines smooth out, and the scars become soft and inconspicuous.

In the present state of our experience, we are still convinced that even in the earliest cases the safest procedure is to excise the palmar fascia completely; because at this stage the subcutaneous fat is still present and the skin is only slightly involved, the result is usually satisfactory. In this way the progress of the disease can be absolutely checked.

In operating on a patient with Dupuytren's contraction great care must be taken to avoid interference with the circulation, as gangrene of the fingers occasionally occurs. Recently Roedelius reported three such cases in which amputation of the gangrenous fingers became necessary. In one case the infiltration with the local anesthetic containing epinephrine was thought to be the cause. If a local anesthetic is used in these cases, our feeling is that nerve block is the method of choice, as infiltration of tissues of lowered vitality with an anesthetic with or without epinephrine may cause local slough and gangrene. The use of an Esmarch bandage in order to give a bloodless field may also have some effect, especially in arteriosclerotic persons. We always endeavor not to apply the bandage too tightly and to keep it on for the shortest possible time. If it is carefully applied above the elbow of a normal person, we have found it safe to leave it in place for an hour and even a little longer, as there is no untoward effect. Probably the condition of the blood vessels also has some bearing on the cause of gangrene. In long-standing, markedly contracted cases, particularly when there is arteriosclerosis, the blood vessels may have become kinked and tortuous, and the straightening of the fingers may disturb the circulation

sufficiently to cause gangrene. The formation of a postoperative hematoma in the palm may cause gangrene of the skin. To these causes may be added rough handling of tissues, infection and, last but not least, dressings that have been applied too snugly. We apply the dressings so that the ends of the fingers can be under constant observation and the circulation checked up. We feel that in these cases it is advisable to tell the patient of the possibility of gangrene before operating, as we also always do before operating for syndactylism. So far we have been fortunate in that gangrene of the fingers has not occurred in any of our cases.

After the excision of the deep fascia, the fingers should be slowly extended with the greatest gentleness, in order to avoid injury to the vessels and other tissues that have been so long contracted. After removal of the tourniquet, checking of the oozing is often difficult, and even if the wound is apparently dry, sometimes a hematoma subsequently forms in the wound. We have found it advantageous to insert at two or three places along the suture line several strands of horsehair which lead down deep into the wound and which are carried out beyond the sea sponge dressing. These drains are drawn out in forty-eight hours without disturbing the dressing and will take care of the ordinary accumulation of blood or serum. If a hematoma forms in spite of every precaution to avoid it, it may be allowed to remain and organize with the formation of considerable thick scar, which eventually will result in a well functioning hand with a somewhat thickened palm, or the clot may be removed. This may sometimes be accomplished by opening a portion of the incision and sucking out the clot with an aspirating nozzle. If this is not successful, as much of the wound as is necessary should be opened and the clot thoroughly removed. Then the wounds should be resutured, a few horsehair drains placed as described and even pressure again applied with a sterile sea sponge. The most rigid asepsis must be maintained during these procedures.

The employment of fat or fascia or fat and fascia grafts between the skin and the deeper structures of the palm, besides their ultimate use, may have considerable effect on checking the oozing from the raw surfaces.

Even from intelligent persons it is extremely difficult to obtain accurate family histories of such conditions as contractions of the hand, but our impression is that if such records could be obtained, the incidence of heredity in Dupuytren's contraction would be considerably larger than our report shows.

In most instances in which both hands are involved and require excision of the palmar fascia, we have found it advisable to relieve the contraction in only one hand at a time, always choosing the one

that is most involved for the first attempt. However, we have occasionally operated on both hands simultaneously with the patient under an anesthetic and with two operators working at the same time.

CONCLUSIONS

The contraction is named after the famous French surgeon Dupuytren, who in 1831 first determined its cause and accurately described the involvement of the palmar fascia.

The disease of the palmar aponeurosis is a focal hypertrophy of the connective tissue originating in the walls of the smallest vessels and ending in contraction. While the etiology is obscure, it seems warranted to conclude that the contraction is of idiopathic origin, that it is most apt to occur in middle age and the senile period, and that it shows a hereditary influence. It occurs in all social classes and is much more commonly found in men than in women.

There is no single constitutional disease with which it is exclusively associated or of which it is a manifestation. In the majority of cases, it does not appear to be specifically caused by trauma or local irritation, though this factor, as well as local or constitutional pathologic conditions, seems at times to have some exciting or contributing influence.

In our experience the incidence of Dupuytren's contraction in patients with diabetes mellitus is considerably higher than in the same number of persons, otherwise comparable, without diabetes.

The diagnosis is frequently confused by those unfamiliar with the condition with flexion of the fingers due to contraction of the tendons and with congenital contractions. Up to the present time, surgical intervention promises the only permanent cure. This is best accomplished by as complete an excision of the fascia of the palm and its digital fasciculi as is practicable.

BIOGRAPHICAL SKETCH OF DUPUYTREN

Guillaume Dupuytren, the son of a poor advocate, was born on Oct. 5, 1777, at Pierre-Buffière, a small town of Haute-Vienne. In 1789, Captain Keffer, a cavalry officer stationed at Pierre-Buffière, obtained permission to take the boy, who was then 12 years old, to Paris. For four years he went to school, distinguishing himself in philosophy, and when he was 16 years old and the time had come to choose a profession, both Dupuytren and his father decided in favor of medicine.

He devoted himself with the greatest zeal to anatomy, and when he was 18 years of age was given the position of prosector at the École de Santé. In 1801, he became head of the department, and two years later founded the Société Anatomique. Dupuytren was not 20 years old when he received his degree of Doctor of Surgery, and when he was 25 he received his first appointment at the Hôtel-Dieu as surgeon of the second class, against great and intensive public competition. In 1808, he became surgeon of the first class, and when Sabatier died in 1811, Dupuy-

tren became professor of operative medicine. After Pellatan, who was then chief surgeon of the Hôtel-Dieu, became involved in an unfortunate affair, Dupuytren succeeded in compelling him to accept the appointment of honorary chief, and he himself realized his ambition and became chief surgeon to the Hôtel-Dieu.

He soon distinguished himself in the department of clinical surgery, and for twenty years controlled the surgical wards like a despot. Percy named him the first of surgeons but the last of men, while Lisfranc dubbed him "The Brigand of the Hôtel-Dieu." Garrison spoke of him as "a shrewd diagnostician, an operator of unrivalled aplomb, a wonderful clinical teacher, a good experimental physiologist and pathologist." Boas regards him "as the most brilliant and fortunate French surgeon of the nineteenth century, equally famous as a keen diagnostician, bold and dextrous operator, fluent and untiring clinician and teacher, a physician cautious in his after treatment, a master and yet prudent in his determination of the indications, an enlightened physiologist, well-versed in normal and pathological anatomy . . . in a word, a man endowed with the rare gifts of his profession."

Dupuytren originated many operations, but his most enduring title to fame was in the field of surgical pathology. He was the first to introduce pathologic anatomy into surgery. His original descriptions of fractures of the lower end of the fibula and contraction of the palmar fascia are classics in surgery. His memoirs on diseases of bones and other phases of surgical pathology were translated by the Sydenham Society in 1847 and 1854.

Toward the end of 1833, Dupuytren suffered an attack of apoplexy, and because of his weakened condition, his friends pleaded with him to seek respite from his arduous labors. His reply was "Le repos, c'est la mort" (Repose, that is death). A chill followed by pleural effusion soon obliged him to relinquish active duty at the hospital. He intended to be operated on by Sanson, but at the last minute refused, saying that since death was inevitable, he would rather die at the hands of God than of man. He passed away on Feb. 8, 1835, at the age of 57.

He was borne to his grave in Père Lachaise by his former students and followed by the most eminent men in science. Great numbers of the poorer class were present at the funeral in grateful remembrance of the abundant benefits for which they were indebted to the chief surgeon of the Hôtel-Dieu.

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UNUNITED FRACTURES

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In the management of ununited fractures, as with all other injuries and diseases of bones, one is dealing with a problem about which there is, generally speaking, not the slightest conception. Bone is usually regarded as an inert substance the function of which is purely mechanical, whereas bone in fact is a most active living tissue and just as vital and essential to life as any organ in the body. In addition to acting as a mechanical support to the body through the skeletal system, bone is the storehouse of calcium, which is just as necessary to the well being of the organism as glycogen of the liver. Also, encased within the bone is the marrow from which the blood, the vital fluid of life, is largely manufactured. Throughout the bone is an orderly system of blood vessels, nerves and lymphatics which supply elements essential to a living tissue and the activities of the living cell.

There is a constant interchange between the calcium-phosphorus in the bone and the calcium-phosphorus content in the blood. In the blood, calcium is held as a calcium-carbonophosphate in a colloidal solution which is precipitated in the bone as a triple calcium phosphate and calcium carbonate. Just how this is brought about is not known, but recently very convincing evidence has been advanced that the parathyroid gland does have a very definite action on calcium in the bones. Overactivity, as manifested by hypertrophy and tumors, or the administering of parathyroid extract (Collip) causes absorption of the lime salts from the bone, thus increasing the percentage of calcium in the blood. This can be carried to such an extent that the skeletal system may become grossly depleted of calcium as manifested in such diseases as osteomalacia, osteitis deformans and osteitis fibrosa cystica. On the other hand, a deficiency in the parathyroid gland will cause a decrease in blood calcium and induce tetany, which is always observed when too much parathyroid tissue has been excised, as in operations for goiter. In the blood of the normal adult the relation of calcium to phosphorus is in the proportion of 10 to 3.5 mg. per hundred cubic centimeters, which, if multiplied, gives a coefficient of 35 that is known as the calcium-phosphorus index. If considerably below or above, there will be a definite change in the quality of the bone which may naturally

affect ossification. Other elements, as magnesium and sulphur, though constantly present in small amounts, may play an important rôle.

An understanding of the physiology of bone repair as manifested in a fracture is requisite to a thorough knowledge of the pathology of fractures. There are two well known theories of the process of bone repair: (1) cellular and (2) physiochemical.

Those who support the former, maintain that bone is formed largely through the influence of an embryonic cell derived from the connective tissue or the mesenchyme of the embryo. There is much difference of opinion as to the origin of this cell, and according to this varied opinion, the cell may be of highly specialized nature, the duty of which is chiefly to produce bone, and is called an osteoblast, or this cell may be a simple fibroblast which exists in all young embryonic connective tissue, as occurs in granulation tissue, or the cell may be derived from the young blood vessels or capillaries which invade healing processes.

Those who support the physiochemical theory maintain that the process is brought about by an unknown physical stimulus which induces calcification in a suitable matrix as is always observed in healing bone. This stimulus may be a ferment, as isolated by Robison, who gave the name of phosphatase to this factor. They do not believe that the osteoblasts or the cells present have any bone-forming function whatever, but that their function is that of the formation of a connective tissue matrix and of limiting or absorbing excess bone. They call attention to the fact that heterogenous bone is formed in other portions of the body in no way connected directly or indirectly with the skeletal system, as the ovary and choroid of the eye. Therefore, in no possible manner could there be present a highly specialized cell capable of producing bone. The source of calcium is believed to be largely from the site of the fracture as suggested by osteoporosis of the fragments, and is thus local and not from the blood stream. However, this does not explain heterogenous bone or the calcification of necrotic areas.

Another ancient question, which is still unanswered, is the rôle of the periosteum in the healing of fractures. This has existed since the time of Duhamel and Haller, the former contending that bone is formed from the periosteum, the latter taking the opposite view, that bone is formed from bone and that the periosteum is only a limiting membrane.

There is not the slightest difference from a practical standpoint whether bone is produced by the cellular or by the physiochemical theory, whether the osteoblast is a highly specialized cell or derived from other sources or what might be the rôle of the periosteum, but the well known evolutionary process of the healing of a fracture is of the greatest importance and may be described briefly as follows:

(1) hemorrhage, (2) formation of blood clot between the fractured surfaces, (3) cellular invasion with the formation of a fine fibrillar network, (4) the formation of a hyaline and periosseous substance and (5) calcification. With the exception of calcification, the process is practically the same as in granulation tissue in the healing of any wound. This process has been compared to the setting of the plaster of paris in the meshes of a crinoline bandage, the crystallization of the plaster corresponding to the precipitation of calcium and the crinoline to the connective tissue matrix.

There are two factors essential to ossification: (1) a hyaline matrix in an area of retarded circulation as a blood clot, and (2) a surrounding area in which there is sufficient blood supply.

Liek's experiments on inducing bone in the kidney are convincing in supporting the truth of these two factors. On ligating the renal artery, bone was induced to form in rabbits in three months, but if a flap of omentum, which has a good vascular supply, was attached to the surface of the kidney, bone was formed at the end of three weeks. He thus caused in the tissues of the kidney an area of sluggish blood supply, and surrounding this area by the omental attachment an abundant blood supply.

The evolution of the various stages of osteogenesis is observed by the fifth day, when there is new bone present, but from four to eight weeks is required before the process is entirely complete. During this time there are two active processes, bone formation and bone resolution. The latter is caused by osteoclasia and osteolysis. Osteoclasia is the action of large giant cell osteoclasts; in bone, the new bone is destroyed by them and also the old bone is invaded, forming irregular cavities into which the new bone forms, causing a firmer attachment or interlocking between the new and old bone of both fragments. Osteoblasts are also thought to possess similar action and by a process of fusion to form osteoclasts. Osteolysis is a chemical process by which excess bone is absorbed by the action of the tissue fluids. Blood vessels invade the new formed bone or callus, at right angles to the shaft, about which are formed layers of calcified connective tissue with the osteoblast caught within, becoming the adult bone cell and thus forming haversian systems which must gradually change their direction to become longitudinal, as in the normal bone. By this process of gradual bone production and resorption a new marrow cavity is also formed connecting with the marrow cavity of the fragments, and the callus becomes organized and a part of the original bone. Too much emphasis cannot be placed on the fact that this entire local process depends on the integrity of the circulation, which, as emphasized by Murray, is derived largely from the surrounding soft tissues and not so much from the

nutrient artery as generally supposed. Both the endosteum and the periosteum play an important rôle in the production of callus, but the part of the endosteum has in the past been underestimated.

If, from any cause, this very delicate and intricate process of callus formation is retarded or interfered with, bone repair will be delayed or there may develop a nonunion.

Nonunion must, in any discussion of ununited fractures, be distinguished from delayed union, as unfortunately, many are submitted to radical and often unnecessary operative measures, when excellent results could be secured by conservative means. A fracture should not be regarded as ununited until the process of repair has ceased and there is an organized status of the tissues involved. As previously stated in articles published in 1924 and 1927:

A fracture is usually classed as ununited when there is free motion between fragments at the end of six months. However, there is no arbitrary time when distinction can be made between delayed union and nonunion. If stability gradually increases, the prognosis for solid union is good. Only after a stationary period has been reached without effort to consolidate can the fracture be designated as ununited.

Ununited fractures at the present time are undoubtedly of more frequent occurrence, which may be considered the sequence to the actual increase in number of fractures as a result of the automobile and other industrial accidents. However, the quantity alone does not account for the increase in fractures which fail to unite. This increase in recent years is probably due to three factors; (1) An increase in the severity of fractures, as evidenced by more compound fractures, more trauma to the soft parts, bones, nerves and vessels; (2) the occurrence of a greater number of multiple fractures, which makes a greater demand on the callus output of the individual, as evidenced by defective union at one or more sites; (3) incompetent and often inadvisable surgery, which has been caused by the evolution in the treatment of fractures to meet the demands of the X-rays. In former years, the physician was content with anatomical alignment, but at present perfect reduction is sought by repeated manipulations, which often fail and impair the natural process of repair. Resort to open operation is employed too frequently, delaying union by mere incision and, in many instances, causing further damage by trauma.

In a series of 4,771 recent fractures there were only 4 in which there developed a permanent status of nonunion in fractures of the long bones. This does not, however, include fractures of the neck of the femur, which is a different equation and not considered in the present discussion.

ETIOLOGY

The cause of nonunion in fractures is constitutional and local. Local causes are by far more frequent, as proved by the fact that union can be induced by efficient local measures in over 90 per cent. Of the remaining 8 or 10 per cent in which union fails after efficient measures, there are still present local factors, as circulatory disturbance

and deficiency in quality of the tissue as induced by excessive scar tissue and dense eburnated bone. In not more than 1 per cent are constitutional factors a probable causative agent. Many diseases are mentioned as possible etiologic factors, the most important of which is syphilis. This, I have found to be a probable factor in a small number, but in cases in which the Wassermann reaction is four plus by far a majority of the fractures will heal uneventfully in normal time. Also, in those few instances I have observed of fractures in persons with parasyphilis as *tabes dorsalis*, union has been prompt and without complication. The fact that nonunion is of frequent occurrence at one or more sites of fractures in those with multiple fractures indicates the probability of there being some general control of callus output in the body, and that when the demand exceeds a limit, failure at some point will occur. Also, in some persons, there is apparently a congenital deficiency in quality that does not permit normal ossification. Just what element may be deficient is not known. There is evidence, however, in the fact that fractures in such cases are either much delayed or do not unite by osseous fusion. This is observed, though rarely, even in children, in whom ununited fractures are notably a more difficult problem than in the adult. In children, bone proliferation is much greater than in adults, and repair very rapid, so that when nonunion does occur there is always some very definite cause, as deficiency in quality which is often of a congenital nature. Such defects usually are corrected as the period of growth ends.

According to Petersen, there may be a deficiency in the inorganic elements of the blood in ununited fractures, as denoted by a decrease in the calcium-phosphorus index. This, however, has not been present in my cases, repeatedly examined, or in those of Kellogg Speed of Chicago, and of Henderson of Rochester, Minn.

The local causes may be classed as: (1) those that interfere with the local blood clot, (2) those that impair circulation and (3) infection. Wide separation of fragments, interposition of soft parts, excessive hemorrhage, injury to soft structures, as periosteum, muscles, nerves and vessels and compound fractures are frequent factors. In pyogenic infection there is formed a solvent for callus and bone which notably retards and often prevents union.

The actual pathologic process of an ununited fracture is the formation between the fragments of a more highly specialized tissue as fibrous tissue and cartilage with which may be associated here and there areas of bone formation, but not sufficient to bridge the fracture. An actual joint may be observed, especially in those of long duration, with an investing cartilage of fibrocartilaginous nature, joint fluid and a capsule. There may be condensation of bone in the fragments or

osteoporosis, the former probably due to a sluggish circulation, the latter to active circulation. When condensation is present the medullary cavity is filled with dense eburnated bone, and the fragments are often hypertrophic for 1 or more inches, often with flaring of the terminal surfaces, which may be in the form of a concavity in one fragment, usually the proximal, and a more or less rounded condyle on the other. Bone atrophy, when present, is apparent by an absorptive process in the trabeculae and deficient bone production in the ends of the fragments which may often become conical.

The factors of bone resorption, osteoclasia and osteolysis, previously described, may predominate, thus causing dissolution of the newly formed callus. This is probably what occurs in those with apparent union which later become angulated or completely separated with decreased amount of callus.

In taking into consideration the physiologic, pathologic and clinical evidences, what are the local factors apparent in the evolution of nonunion?

1. By a loss of blood clot and defective circulation, bone production may be limited to the extremities of the fragments; thus there is condensation of bone with highly developed connective tissue and cartilage between the fragments.

2. An intense reaction, from excessive damage, may induce an inflammatory reaction with incident increased blood supply in the area of callus formation. Bone atrophy ensues and, as a medium of sluggish circulation or blood clot is prevented, adult fibrous tissue is formed between the fragments.

3. The local process may be normal, but the reaction of the surrounding tissues to excessive trauma may be such that invasion of granulation tissue with development of adult fibrous tissue may overcome the natural process of bone repair.

4. Gross injuries to nerves do not apparently impair callus, but the nerve is usually traumatized at the site of fracture and not above. Probably imbalance of the vasomotor system may impair osteogenesis, as Leriche reports union after sympathectomy in ununited fractures.

5. Inefficient fixation in fractures of the shaft of long bones prevents callus by frequent movement and interference with the delicate process of repair. This, however, is not so much a factor in the extremities of the bones, as callus is formed more rapidly in cavernous bone.

6. Impairment of circulation to the fractures may obviously be caused by the aforementioned factors.

The clinical symptoms of nonunion are too obvious for description, except in those rare cases in which the degree of union is greater than in the average case. This type is most frequent in the leg when only the

tibia fails to unite with solid union of the fibula. In these the movement between the fragments is so slight that even with great care it is difficult to detect. The symptoms are tenderness at the point of fracture, with pain and swelling when standing or walking, thus causing material disability. The roentgenogram will usually demonstrate a definite fracture line, regardless of the time which has elapsed since the fracture. These symptoms may persist for years, and often the opinion of the attending physician has been given that the union is solid, the result is excellent and that there is no reason why the patient should not return to his former occupation.

TREATMENT

The treatment for nonunion is that of every major surgical problem. The patient should be placed in the best possible physical condition, and

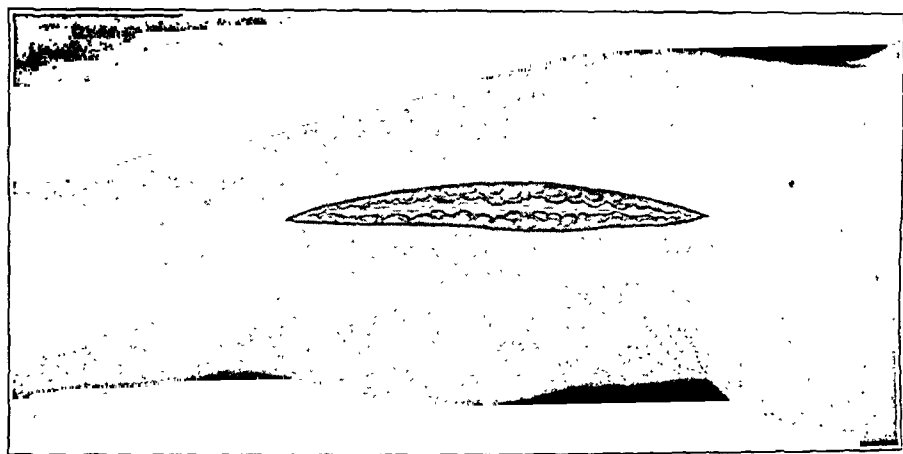


Fig. 1.—Skin incision on the lateral surface of the thigh in an operation for ununited fracture of the femur.

any local or constitutional defect eliminated which may be observed by a careful routine examination. The greatest preventive measure, however, is the proper local treatment of every fracture, with recognition of the fact that one is dealing not alone with a traumatic severance of bone, but invariably also with more or less injury to the soft parts, as muscles, fasciae, arteries, nerves and lymphatics.

The keynote in treatment of every fracture should be end-to-end reduction, maintenance of reduction until union is solid, with conservation of function. This can be accomplished in over 90 per cent by manual reduction followed by efficient fixation, and, in only a small number are such measures as open operation and skeletal traction or apparatus required. There is undoubtedly a greater demand for better anatomic reduction of fracture. Accordingly, more fractures require

radical measures, and when these are necessary they should be employed. However, too much attention in the treatment of fractures is given to the methods required in only a small percentage, and there is too little given the development of efficient manual reduction and fixation. As a result, often comparatively simple problems are complicated by radical measures.

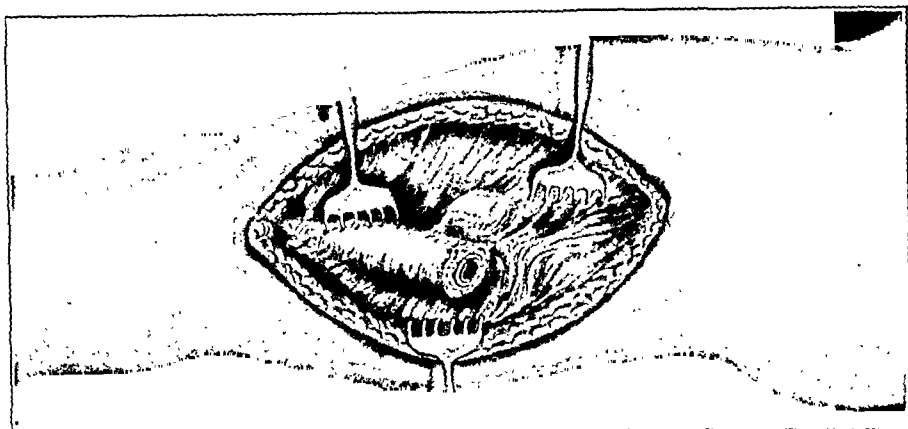


Fig. 2.—The subcutaneous tissue, fascia and muscles are divided and the soft tissues retracted; the fragments of the femur are exposed but the muscles are stripped from the bone as little as possible. The end of the distal fragment has been denuded of fibrous tissue and the medulla freely opened with a bone drill.

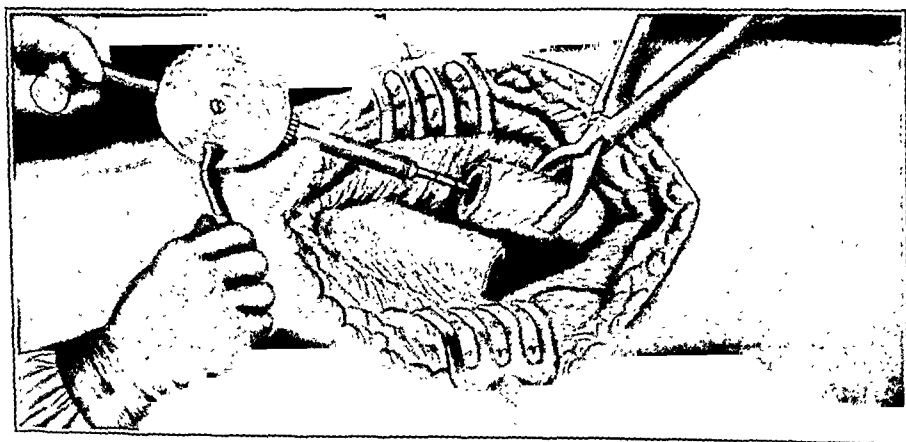


Fig. 3.—The end of the upper fragment is likewise denuded and the medullary cavity opened using a bone drill.

There is no specific therapy except that to raise the stamina of the patient. Parathyroid extract has been advised with the idea that calcium is taken from the bones, and the percentage in the blood is thus materially increased and utilized in callus formation. However, the same physiochemical process that extracts calcium from the bone may also remove calcium from callus; thus in all probability such measures

bone graft which must be applied with due consideration to the principles of bone regeneration and repair. There are five types of transplants that have been employed by various surgeons in ununited fractures: (1) medullary, (2) osteoperiosteal, (3) chip, (4) inlay and (5) onlay.

All surgeons describe the method they employ as "the physiologic method," but in reality, the physiologic method is the one that will give

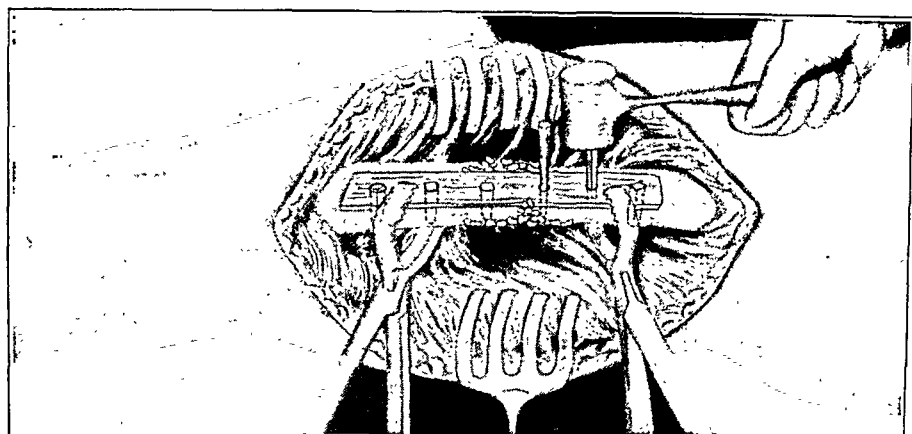


Fig. 8.—The drills are removed one at a time and an autogenous bone nail driven into each hole. Cancellous bone is packed about the graft and around the site of the fracture.

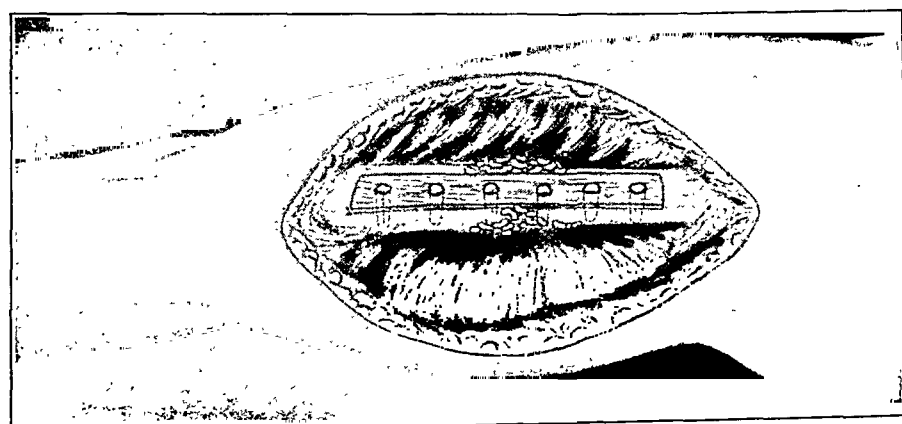


Fig. 9.—Solid fixation should be secured so that when the operation is completed there will be no motion between the fragments.

the highest percentage of solid bony union in the shortest space of time. Like many discoveries in medicine, an operative procedure is worked out that gives the best functional result, and there are always forthcoming theories to conform better to physiologic principles. Quinine was employed for many centuries before its action in malaria was known; the same may be said of mercury in syphilis. Ununited fractures were

unsuccessfully treated by paring of the fractured surfaces and inefficient internal fixation, as previously mentioned. As more knowledge of the physiologic principles of bone repair has been gained, it has been proved that in nonunion there is a local deficiency which is best overcome by the addition of new bone which promotes osteogenesis. The problem is both physiologic and mechanical.

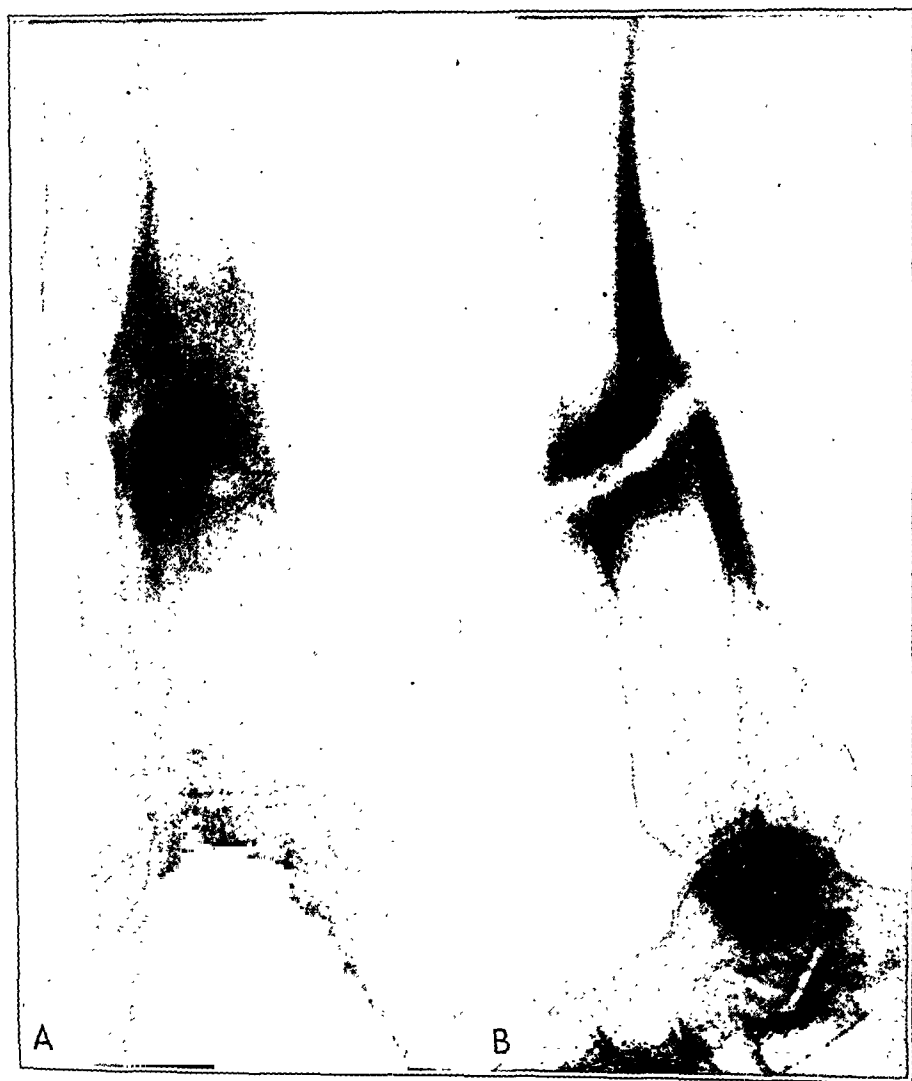


Fig. 10.—*A*, delayed union in fracture of the tibia, anteroposterior view; *B*, same as *A*, lateral view.

Of the five methods mentioned, one has no place in ununited fractures, and that is the intramedullary graft, as the pressure within the canal destroys the endosteum, which is an important reparative agent. The chip and the osteoperiosteal graft may be useful adjuncts, but of themselves are insufficient. Albee has proved the efficiency of the inlay method. I have employed a method which was first described in 1923,

to which I gave the name of the onlay graft. It is believed that this graft meets better the physiologic requirements which are: (1) absolute fixation and (2) the promotion of osteogenesis. By no other method has fixation been so uniformly accomplished. The operative technic has continued essentially the same since the first description in 1923, which is as follows:

An ample incision is made through the skin in order to expose each fragment, when possible, for 4 inches (10 cm.). Routine dissection is

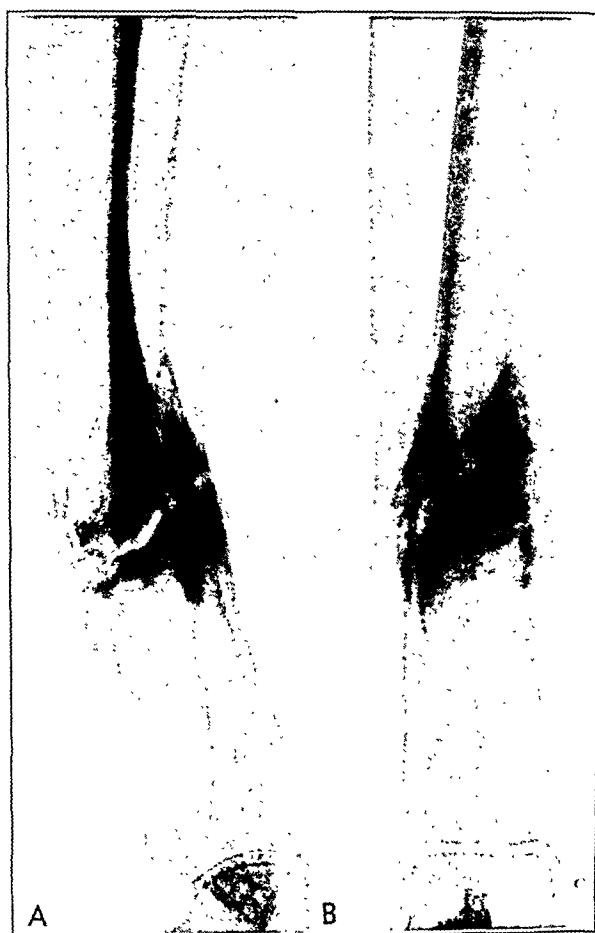


Fig. 11.—*A*, fracture of the tibia ten months after operation, anteroposterior view. The onlay bone graft was not employed. The ends were freshened and cancellous bone placed between the fragments. Union of the fracture is solid. *B*, same as *A*, lateral view.

made to the site of fracture; all intervening scar and fibrous tissue is removed; the fragments are pared with chisel or motor saw, and each medulla is reamed out until normal marrow tissue is reached. The fragments are rotated until the normal relation has been restored. An incision is made through the periosteum of each fragment, for several inches, depending on the length and the anatomic location. The peri-

osteum is stripped from $\frac{1}{2}$ to $\frac{3}{4}$ inch (1.3 to 1.9 cm.) from the circumference, leaving attached, as much as possible, the soft parts from which circulation is derived. With a chisel, "shavings" are removed from the circumference until there is a continuous flat surface, for 3 or 4 inches (7.5 or 10 cm.), when possible, on each fragment. A broad flat massive graft is taken from the tibia, which should be of sufficient length, breadth and dimensions to secure firm fixation. With a motor saw, the graft is split longitudinally through the edge or small diameter into two parts, a strong outer plate consisting of dense bone or cortex, and an inner, the endosteum. A strip of endosteum is placed within the medulla, bridging the site of the fracture as reduction is made, normal marrow tissue rich in osteoblasts being thus restored. From the outer plate, or as a separate graft, a strip of dense bone is taken, from which six or eight autogenous bone nails are made, of appropriate size. This is accomplished by the aid of a rotary file attached to the motor saw and a metal gage to measure dimensions. The strong outer plate is held to the flat surface of the bone, passing across the site of fracture. Three or four drill holes are made through the graft and each fragment, into which the autogenous bone nails are driven. The remainder of the endosteum is broken into small particles and placed with the "shavings" about the site of fracture.

Spongy bone is always available from the upper extremity of the tibia and can be obtained by a sharp bone curet. About six pieces are removed in this manner and applied around the area of fracture. Spongy bone is more proliferative than any other type of graft, being successful in 100 per cent in an operation which I have devised for a type of paralytic foot. By this method, solid fixation is attained so that when the operation is complete no motion is apparent. The transplantation of endosteum to the medulla and cavernous bone about the fracture is an excellent method to promote osteogenesis. Henderson employs a similar method which differs from the one described in that he employs beef bone nails, removes the cortex to the medulla and does not use the transplant of endogenous and spongy bone.

The after-treatment consists in complete fixation by a plaster of paris cast or efficient splint which remains for a period of eight weeks. When this is removed a convalescent splint is applied, usually in the form of a leather corset to reproduce the cast. Joints are usually incorporated, so that active and passive motion may be carried out as soon as feasible. With rare exceptions, no motion could be detected at the site of fracture after the operation had been completed, and union was apparently firm at the end of eight weeks, but from previous experience with delayed union and ununited fractures protection of some form is required for at least six months after the operation. The reason for this continued protection is explained on a physiologic basis. In the lower extremity,

weight-bearing is often gradually permitted by the aid of a Thomas knee brace, and apparatus is not discarded until the roentgenogram demonstrates that the callus is organized.

The bone graft must not be applied under tension, or disintegration will occur with separation or fracture at the point of greatest stress, and undoubtedly this is a factor in many of those cases in which there is a fracture of the graft at the site of the original fracture. I have repeat-



Fig. 12.—Ununited fracture of the radius.

edly observed such behavior when a graft has been used for conditions other than ununited fractures; for instance, in bone grafts to the spine, if the transplant is placed under tension to conform to the kyphos or scoliosis, disintegration always occurs with fracture at the point of greatest stress. Also, a graft may be placed in a spine without tension, but after an increase in a destructive process, there may be gradual bending or kyphos with stress on a graft. In such instances there will be disintegration at point of stress, unless there has been sufficient proliferation of the graft itself.

Excessive scar tissue must be excised, and, if there is extensive involvement of the skin with adhesion to the bone, this must be dissected and the wound closed with normal soft tissues of considerable thickness investing the bone. If this cannot be accomplished by plastic arrangement, a pedicle flap or other type of skin grafting should be employed, and the operation on the bone deferred until the soft parts have entirely healed. This dense scar tissue about a fracture, not only is



Fig. 13.—Same as figure 12, after operation. Union is solid.

conducive to sloughing after operation and infection, but prevents revascularization of the transplant and also of the area of the ununited fracture.

Ununited fracture in bone dense and eburnated, as after extensive osteomyelitis, materially lessens the chances of establishing osseous union, and relighting of severe infections is not uncommon. Such cases are more common following pathologic dissolution after improper treatment for osteomyelitis. In infected compound fractures, the fragments are invaded for only a short distance and the onlay graft can be applied

to normal bone above and below with less danger of stirring up a latent infection.

There should be no interference in the after-treatment with the evolutionary process of healing, otherwise there may be impairment of osteogenesis with stimulation of the forces of bone resorption which is a part of the process in bone repair. Bone production and absorption are well balanced in the normal callus. However, if this balance is disturbed from any cause, there may be rapid bone disintegration, and a fracture that is apparently united may separate. This is also true in all fractures, but as healing in ununited fractures is retarded when compared to fresh fractures, a loss of balance can more easily be produced.

ANALYSIS OF CASES

Sufficient time has now elapsed since the first report in 1923, to make a final report as to the end-results in 104 cases. The first onlay graft by the foregoing technic was carried out over ten years ago. The important facts of interest may be enumerated as follows:

END-RESULTS IN ONE HUNDRED AND FOUR CASES

Males	89
Females	15
Ages 5 to 62
Length of time since fracture 6 months to 4½ years
Cases in which there had been from 1 to 4 previous operations	44
Number of cases in which onlay transplants were used.....	104
Number of bones in which onlay transplants were used.....	125
Solid union	95 cases
Solid union	116 bones
Percentage of solid union induced in 104 cases.....	91.5
Percentage of solid union induced in 125 bones.....	92.8
Number of patients above 50 years of age.....	12
Failures in those above age of 50.....	none
History of compound fractures.....	22
Failure in cases with history of compound fractures.....	1

POSTOPERATIVE INFECTIONS

Number of cases	17
Osseous union induced	16
Sequestration of part of, or the entire graft.....	8
Failure of union after sequestration.....	0
Cases with history of a previous pyogenic infection.....	20
Cases in which infection was apparently lighted up by operation..	4

RESULTS OF ONLAY GRAFTS IN DIFFERENT REGIONS IN ORDER OF OCCURRENCE

Humerus	
Total	30
Solid union	29
Failures	1
Tibia	
Total	27
Solid union	25
Failures	2
Radius .	
Total	13
Solid union	12
Failures	1
Ulna	
Total	10
Solid union	9
Failures	1
Radius and ulna	
Total	21
Solid union	19
Failures	
radius	1
ulna	1
Femur	
Total	19
Solid union	17
Failures	2

Fresh fractures should be estimated according to their occurrence in extremities and not in the number of bones involved; for instance, a fracture of the femur and a fracture of the humerus in the same person are two fractures or cases as they involve two different mechanical problems, but a fracture of both bones of the leg, forearm or ribs should be considered as *one* as it involves only one problem. However, in estimating the results of ununited fractures, especially those of the forearm, in which there are two surgical procedures and two transplants in which one may succeed and one may fail, one must also consider the number of bones involved. For instance, in no case of fracture of both bones of the forearm was there a failure of union in both bones, but in two cases there was a failure of union in the radius. These could not be classed as total failures or as perfect results, but possibly as partially successful. However, to evaluate and elucidate better, the estimate has been made separately of the number of cases and also the number of bones involved.

The chances of success in bone grafts is thought to be less as age advances, but it is interesting to note that in this series in the twelve patients above the age of 50 the grafts were 100 per cent successful. In the oldest patient, aged 62, nonunion had existed for seven months. Union not only occurred uneventfully after operation, but this man was

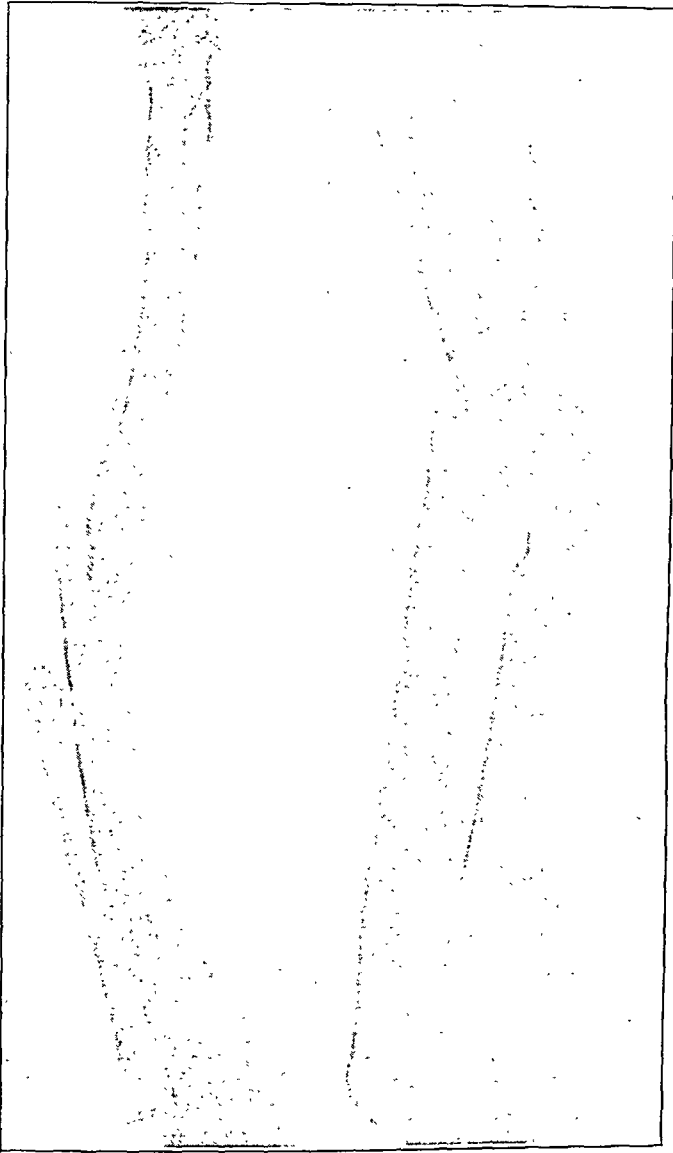


Fig. 14.—Ununited fracture of radius and ulna.

able to return to his former occupation as a laborer on the railroad. Of the 104 cases of ununited fractures, 22, or approximately 26 per cent, were compound, which is surely most suggestive, if not absolutely conclusive, that compound fractures have a definite causative relation to ununited fractures. Of the 22 ununited fractures which gave a history of being originally open or compound, there was only one in which

union failed to be induced. Results were successful in 96 per cent. Only those in which there was frank pus with definite constitutional symptoms of a pyogenic infection are considered in the group of infections. Union was induced regardless of an intense infection in 16 of the 17 infected cases. In 9 the graft remained intact, while in 8

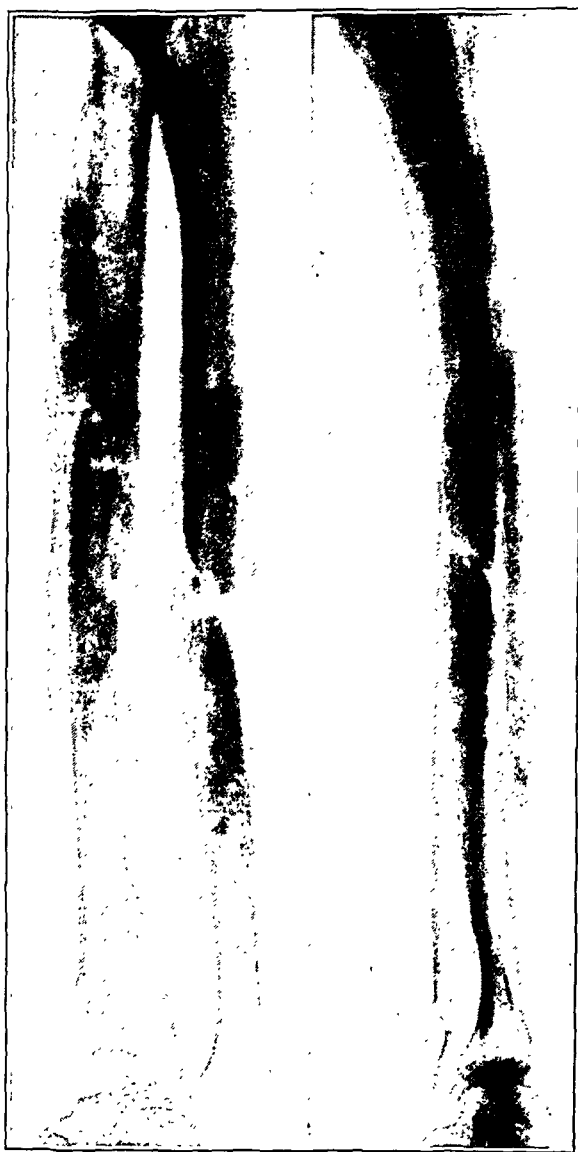


Fig. 15.—Same as figure 14, after operation. Union is solid in both bones.

there was sequestration of a part or the entire transplant. Osseous union was induced in these 8 cases regardless of the infection and sequestration. However, the graft functioned for sufficient time to induce union in 94 per cent. In other words, infection did not materially affect the end-result as regards union.

In this series there were nine cases in which union failed by onlay method. One occurred in a child, aged 5, probably with congenital deficiency in quality of the skeleton, as the fracture was of the green-stick type in the lower third of the leg with no displacement. Also in this case there was a history of other obscure bone disease in the family. However, no specific abnormality could be discovered after a most careful examination. In two cases with nonunion of both bones



Fig. 16.—*A*, ununited fracture of humerus showing wide separation of fragments, anteroposterior view; *B*, same as *A*, lateral view.

of the forearm, fusion was induced in the ulna with failure in the radius; the function, however, in each patient was so satisfactory that further operative measures were declined. The onlay graft was employed in other cases not included in this report, ununited fractures of the clavicle and congenital fractures. The structure of the clavicle, the mechanical problem involved and the frequency of occurrence of nonunion are so different from those of the long bone that a separate classification is given. Congenital fractures are obviously entirely different from a physiologic and pathologic standpoint. Of the three ununited fractures

of the clavicle one was successful and two failed. There were two congenital fractures in which an onlay graft taken from the tibia of the mother was used. Both were in very young children, the ages being 27 months and 2 years, respectively. In one the result was solid union with perfect function and length, while the other failed.

A careful review has been made of serial roentgenograms at intervals of approximately thirty to sixty days for the first six months, and in

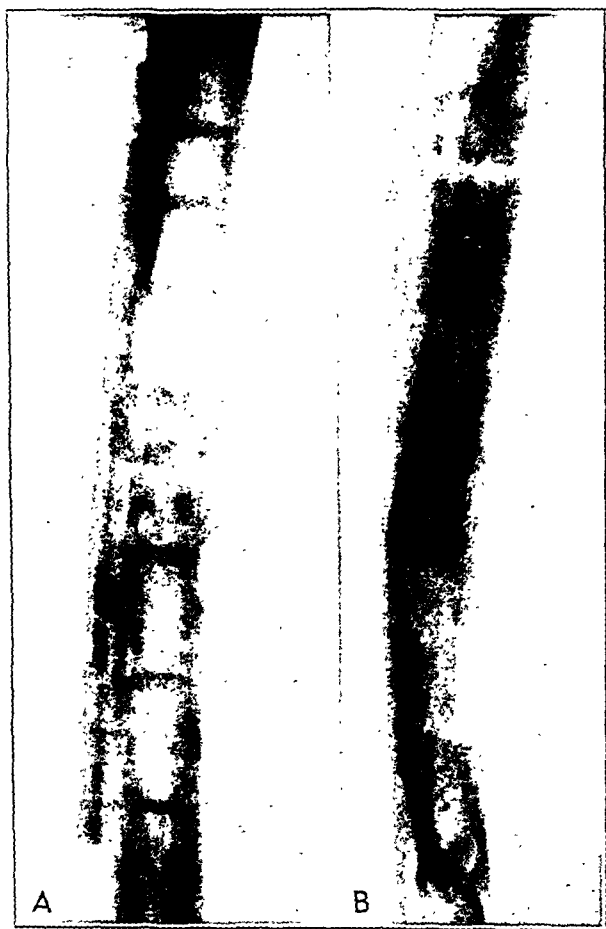


Fig. 17.—*A*, bone graft to the humerus showing solid fixation, eight months after operation, anteroposterior view; *B*, same as *A*, lateral view.

many cases until the elapse of two years. The appearance of the reaction in the fragments of atrophy and condensation has been previously described. When there was satisfactory application, as denoted by close contact of the graft fragments, there was no change in density or structure of the graft which apparently fused to the host, increased in size and became gradually assimilated. The bone nails gradually disappear, but there is usually permanent evidence of the graft, as denoted by an increase in diameter of the shaft. In those cases with extensive bone

atrophy, union was secured, though delayed, evidently from the fact that fixation was not as firm. In many, proliferation of the transplanted endosteum and spongy bone about the site of fracture was quite apparent by the end of eight weeks. In a small number, satisfactory approximation had not been maintained between the graft and the shaft of the bone, over a portion of the graft. In these there was definite evidence of absorption and disintegration, as denoted by enlargement of the screw holes, and punched-out areas in the graft were not in contact. But, at

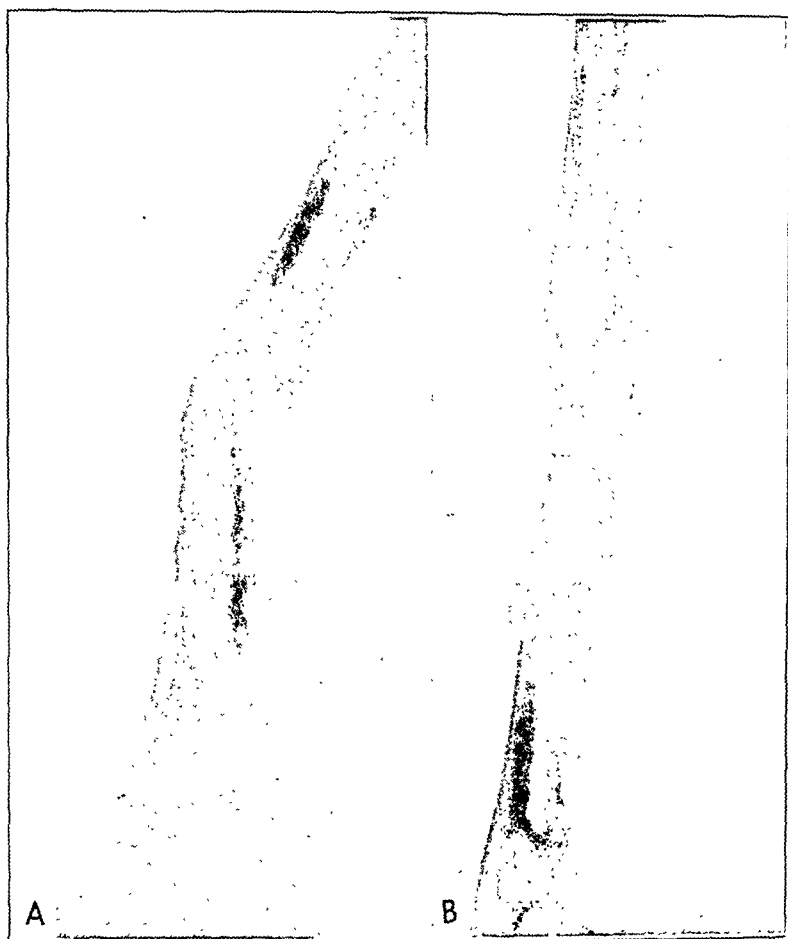


Fig. 18.—*A*, ununited fracture of the humerus showing osteoporosis and atrophy of the ends of the fragments, anteroposterior view; *B*, same as *A*, lateral view.

those parts where there was approximation, the integrity of the graft was not involved and fusion continued. This did not affect the end-result, except that it was thought necessary to continue the use of external apparatus for a longer period of time.

In those in whom there was a primary infection and in those in whom an old infection was lighted after operation, there was apparent at the end of about sixty days a gradual disintegration of the graft with absorption of a portion and in eight cases sequestration; often there was

also evidence of new bone formation, especially along the line of the fracture where endosteum and spongy bone had been transplanted. Fixation, however, was usually maintained for a sufficient time to permit osseous union of the fracture so that the function of the graft was accomplished. The graft, or a portion thereof, in such cases, acted partly as a foreign body, but it is believed that an autogenous graft, even though infected, is better tolerated by the tissues than other foreign material.



Fig. 19.—Bone graft to the humerus, six months after operation. Union is solid.

In a small number of cases the wounds did not heal by primary intention, as evidenced by a persistent drainage for several weeks. Whether these should be classed as mild infections or due to undue hemorrhage from the bone with persistent seepage of serum is a moot question. At any rate, such a status is often observed after extensive operations on bone. In this type the roentgenogram demonstrated osteoporosis of the graft similar to the changes previously described when mechanical approximation was not obtained. Also such changes were occasionally

seen when there was primary healing of the wound, but in by far the greater majority the graft apparently assumed an active part in physiologic bone construction.

The physiologic action of the graft has long been a debatable question, but from the number of transplants I have had the opportunity of exploring, and from clinical experience, I am convinced that the graft may act in two ways. 1. In a large percentage the transplants live and act as living bone; this is often in evidence by the roentgenogram as early fusion to the fragments, and also at exploration by the fact that the physical character of the graft does not change, but is vascularized and firmly united throughout its osseous bed. 2. The graft may partially or entirely disintegrate, only acting for a time mechanically until fusion is accomplished by the fragments. In such cases the graft may be substituted by an ingrowth of the surrounding bone or become osteoconductive according to the theory of Barth. The action of the graft depends entirely on the reestablishment of the circulation. In those in whom vascularization occurs early, the transplants become active living bone, and in those in whom vascularization is deferred, there will be disintegration and substitution by the adjacent bone. Much, of course, depends on the efficiency with which the transplant is applied. The graft also probably acts as a local source of calcium.

Union in ununited fractures is secured by two different processes: functional adaptation of the graft as may be denoted by hypertrophy, and by the union of the fragments themselves. In those instances in which osteogenesis is exceedingly deficient in the fragments, union must be accomplished largely by graft alone, with a gradual fusion of the fragments by a process of functional adaptation along the lines of stress. In such cases protection must be continued for a longer period of time. In most instances, however, union is also induced between the fragments, but is much slower than in fresh fractures, therefore, requiring the services of a graft which, in addition to promoting osteogenesis, also is able to hold the fragments absolutely fixed.

CONCLUSIONS

1. Union is accomplished in a shorter space of time by the onlay transplant, as evidenced by the fact that no motion can be detected from the time that the operation is completed.

2. Earlier movement is permitted in adjacent joints and thus function is conserved.

3. The onlay graft actually increases the dimension and strength of the bone, the circumference is maintained intact and new bone is added thereto.

4. Even in severe infections, solid union is secured by the onlay graft in 94 per cent of the cases; thus infection does not apparently affect the end-result after this method.

5. The only criticism that has been made is that the operation is too technical or difficult, requiring a well trained team of at least two experts and three assistants, but the means are surely justified if the percentage of good results can be thereby increased.

6. In any method selected, all of the physiologic principles of bone repair and bone transplanting, as well as the minute and the gross pathologic process of an ununited fracture, must be given due consideration in the treatment, if the maximum percentage of satisfactory results is to be obtained. It is my belief that the onlay graft conforms better than any other to the physiologic process of repair.

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THERAPEUTIC VENOUS OCCLUSION

ITS EFFECT ON THE BLOOD FLOW IN THE EXTREMITY IN ACUTE ARTERIAL OBSTRUCTION

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Artificial or therapeutic obstruction to the venous return from an extremity in which the arterial supply has been accidentally interrupted has been increasingly adopted as a means of lessening the usual high incidence of gangrene and muscular disturbances. This procedure has been developed during the present century, and its history was very clearly presented by Brooks¹ in his review of the subject in 1929. For the purposes of this paper it is sufficient to say that the clinical studies of Makins,² Sehrt,³ and Propping⁴ and the experimental work of Drummond,⁵ Brooks and Martin,⁶ Holman and Edwards⁷ and others have been responsible for its widespread use in the treatment of patients with sudden occlusion of a healthy artery.

Such features of the clinical and experimental studies as have a bearing on my experimental work will be presented. The use of the procedure in chronic obliterative diseases of the arteries and its application in the treatment for arteriovenous aneurysms will not be discussed.

In summing up the experience of the British Army Medical Service in the district where he was working during 1915 and 1916, Makins presented figures on 172 cases of injury to the arteries of the extremities in which a comparison was made between ligation of the artery alone and ligation of both the artery and the vein. Efforts were made to rule out gangrene due to anaerobic infection. The table reproduces his figures. To them I have added the percentage columns.

Submitted for publication, Aug. 2, 1931.

From the Department of Surgery of the University of Chicago.

This work has been conducted under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Brooks, Barney: *Surgical Applications of Therapeutic Venous Obstruction*, Arch. Surg. **19**:1 (July) 1929.

2. Makins, G. H.: *On Gunshot Injuries to the Blood Vessels*, New York, William Wood & Company, 1919.

3. Sehrt, E.: *Med. Klin.* **12**:1338, 1916.

4. Propping, Karl: *München. med. Wchnschr.* **64**:598, 1917.

5. Drummond, H., quoted by Makins (footnote 2, p. 105).

6. Brooks, B., and Martin, K. A.: *Simultaneous Ligation of Vein and Artery*, J. A. M. A. **80**:1678 (June 9) 1923.

7. Holman, E., and Edwards, M. E.: *A New Principle in the Surgery of the Large Vessels*, J. A. M. A. **88**:909 (March 19) 1927.

Makins stated that the "table does not generally imply gangrene '*en masse*,' but in many cases a very limited amount confined to digits or patches of skin." His study was largely responsible for the acceptance of the principle of simultaneous ligation of the vein by the Interallied Congress of Surgeons in 1917.

In Germany, Sehrt reported that in the lower extremity, when the artery alone was ligated, gangrene occurred in 20.4 per cent of the cases, whereas it was seen in only 9 per cent when both the artery and the vein were tied. His figures for the occurrence of gangrene in the upper extremity were respectively 7.8 and 0 per cent. Propping reported two cases of ligation of the common carotid artery in which the internal jugular vein was also ligated, in one at the time of the ligation of the artery and in the other at a later date. In neither did symptoms of brain

A Comparison of the Results of Ligations of the Artery Alone with Those of Simultaneous Ligations of Artery and Vein

Artery	Artery Alone				Artery and Vein			
	Number of Cases	Good Result	Gangrene	Percentage of Gangrene*	Number of Cases	Good Result	Gangrene	Percentage of Gangrene*
Subclavian.....	4	3	1	25.0	1	1	..	0.0
Axillary.....	6	5	1	16.6	4	4	..	0.0
Brachial.....	13	10	3	23.0	1	1	..	0.0
Femoral.....	32	24	8	25.0	32	25	7	21.0
Popliteal.....	24	14	10	41.6	28	22	6	21.4
Tibial.....	4	4	..	0.0	1	1	..	0.0
Carotid.....	18	12	6	33.3	4	3	1	25.0
Total.....	101	72	29	28.0	71	57	14	19.7

* All the percentages were added to the table by me, except the total percentages, which appear in Makins' original table.

disturbance develop. This author made some studies on hydrostatics, using a rubber glove to represent the venous and capillary beds and varying the inflow and the resistance to outflow, which led him to believe that ligation of the vein restores the "circulatory balance" between inflow to and outflow from the extremity.

In the laboratory, Drummond found in the cat that when the main artery and vein supplying a loop of bowel were ligated, the incidence of gangrene was less than when the artery alone was occluded. Brooks and Martin, using rabbits, found that when the common iliac and external iliac arteries were ligated proximal and distal to the origin of the hypogastric artery, gangrene developed in 71.5 per cent of animals, whereas in a second series in which there was added to this procedure ligation of the common iliac vein, the incidence of gangrene was only 33.3 per cent. Holman and Edwards observed that when the common iliac artery and the inferior vena cava were ligated simultaneously in eighteen rabbits, only two cases of gangrene developed, and that none occurred in ten rabbits in which the common iliac and external

iliac arteries and the inferior vena cava were simultaneously obstructed. In this group of twenty-eight animals, gangrene was found in only 7.1 per cent.

In an effort to explain the beneficial effect of venous obstruction, studies were made to observe its influence on the flow of blood through the extremity.

Brooks and Martin, using anesthetized dogs, compared the temperatures of the tissues of both lower limbs (thigh and foot) with thermometers inserted into the substance of the limbs. They used room and rectal temperatures as control records. When the left iliac artery was ligated, the temperature of the left thigh and foot fell, whereas the other temperatures remained essentially unchanged. After the temperatures reached equilibrium, the left common iliac vein was ligated. A further fall in the temperature of the left thigh and foot occurred. These authors attributed the decrease in the temperatures of the left leg to a diminution in the flow of blood through the extremity. From this they concluded that ligation of the vein decreased the flow of blood through the extremity, and that the beneficial effects were due to some other cause. The explanation was to be found, they believed, in the elevation of the peripheral blood pressure which was observed on experimental animals by Van Kend,⁸ Hooker,⁹ Brooks and Martin and others. It was the opinion of the latter authors that the maintenance of a certain minimum peripheral blood pressure may be necessary to force blood through nonrigid, collapsed capillaries and perhaps to preserve the flow of nutrient material from the capillaries to the tissues; that when a major artery is ligated, the pressure falls below this critical level and is restored by the ligation of the concomitant vein. Brooks amplified this position in 1929.

On the other hand, Holman and Edwards stated the belief that ligation of the vein increased the flow of blood through the extremity, and that when the venous return was obstructed proximal to the point of arterial occlusion, the increase was greater than when the concomitant vein was ligated. Their opinion was based on experiments in which the superficial femoral artery in anesthetized and heparinized dogs was ligated and cannulated distal to the ligature. The rate of flow of blood from the distal stump through the cannula was measured in cubic centimeters per minute, and it was taken to represent the changes that were occurring in the blood flow through the leg. In one experiment with an animal weighing 10.4 Kg., the initial flow was 0.9 cc. When the superficial femoral vein was ligated, it rose to 2 cc. Ligation of the common iliac vein increased the flow to 10 cc. (an increase of over

8. Van Kend, quoted by Makins (footnote 2, p. 103).

9. Hooker, D. R., quoted by Halsted (footnote 15, p. 25).

1,000 per cent), and a further slight increase was noted on ligation of the inferior vena cava just proximal to its origin.

From these observation and their studies on the decreased incidence of gangrene in rabbits after proximal venous occlusion, Holman and Edwards concluded that obstruction of the venous return proximal to the point of arterial occlusion serves as a superior means of reducing the incidence of gangrene, largely because of the increase in blood flow which, they believed, occurred after its use.

Somewhat later Theis¹⁰ compared the flow of blood from the proximal end of the superficial femoral artery with that from the distal end both with and without ligation of the common iliac vein. Records were taken immediately after ligation and for varying periods afterward up to six weeks. Large dogs were used, and the operative procedure was carried out by means of aseptic technic. This author found that the normal flow of blood from the proximal end of the femoral artery averaged 240 cc. per minute. After ligation of the vein, the immediate per minute flow from the distal end of the artery was 48 cc. Ten minutes later it had risen to 51 cc. and one hour later to 54 cc. After the lapse of three weeks it was 96 cc. These results were compared with the effect of ligation on the superficial femoral artery alone on the opposite side of the same animal. Whereas the immediate flow from the proximal end of the femoral artery was the same¹¹ as that on the opposite side, the flow from the distal end was only 39 cc. After one hour the latter had increased to 54 cc. per minute, which was identical with that for the like period on the opposite side. Three weeks after ligation of the artery alone the flow had risen to 136 cc., in contrast with 96 cc. when both the artery and the vein were ligated.

From this and roentgen studies of the arterial circulation following injection of Hill's opaque mass, Theis concluded that the final collateral circulation is much better developed when the artery alone is ligated. Nevertheless he believed that "with sudden occlusion of a large artery . . . the immediate improvement in the collateral bed due to ligation of the concomitant vein is needed to maintain the vitality of the limb." This author also accepted increased discharge of blood from the distal end of a ligated femoral artery as evidence of an increase in the blood flow through the extremity.

Finally, in 1929 Brooks pointed out that instead of measuring the flow of blood through the limb, Holman and Edwards had determined only the amount of blood delivered by the collateral arterial circulation

10. Theis, F. V.: Ligation of Artery and Concomitant Vein in Operations on the Large Blood Vessels, *Arch. Surg.* 17:244 (Aug.) 1928.

11. These figures do not actually represent the flow of blood through the superficial femoral artery at this point, because, under the conditions of the experiment, all arteriolar and capillary resistances have been removed.

to the distal arm of the femoral artery, and that when the vein was ligated the resulting rise in the venous blood pressure increased the resistance of the venous and capillary beds to the flow of blood and thereby sidetracked the blood coming through the collateral circulation from its normal channels into the open, low resistance femoral artery.

From a study of the work just reviewed it appeared that the divergence of opinions arose from the use of indirect methods for the determination of the blood flow. It seemed possible that the subject might be clarified by employing the recently devised, direct, continuous volume flow apparatus of Montgomery and Lipscomb.¹² To this end the experimental work reported in this paper was carried out. A preliminary report was made on part of this work in 1928.¹³ The final report has awaited perfection of the instrument.¹⁴

METHOD

Dogs weighing from 12 to 25 Kg. were anesthetized by the administration of sodium barbital, from 250 to 300 mg. per kilogram of body weight by stomach tube, or from 150 to 250 mg. per kilogram of body weight intravenously. In each animal one carotid artery, the right iliac and the common iliac veins, and the inferior vena cava at its origin were dissected out, care being taken to ligate all visible bleeding points. The animal was then allowed to remain undisturbed for from fifteen to thirty minutes to increase the assurance of coagulation of the very minute vessels. Heparin, 30 mg. per kilogram of body weight dissolved in 15 cc. of distilled water, was then injected intravenously as an anticoagulant. The systemic blood pressure was recorded from the carotid artery. The inlet and outlet arms of the volume flow apparatus were attached respectively to cannulas placed in the proximal and distal arms of the iliac artery. In a few cases T cannulas were placed in continuity in the superficial femoral artery and vein in order that the pressures in these vessels might be obtained before and after arterial and venous occlusion was done, and their side arms were connected with the usual form of mercury blood pressure manometer.

Ten experiments were performed. They were divided into two series. In the first, the systemic (carotid) arterial blood pressure, the superficial femoral arterial and venous blood pressures and the volume flow of blood through the iliac artery were recorded. In the second, the systemic (carotid) arterial blood pressure and the volume flow of blood through the iliac artery alone were obtained. The latter series was planned because it seemed probable from experience that the placing of T cannulas in the femoral vessels disturbed the mechanism of the vascular system considerably. This was especially noticeable in certain large animals in which the free iliac arterial blood flow was much below the expected. It was also found that the reactive hyperemia which followed temporary obstruction of the iliac artery while the instrument was being put into place was quite marked. To control this factor the blood was allowed to flow through the instrument for at least the length of time of the obstruction of the artery before the initial records of the arterial flow were recorded.

12. Montgomery, M. L., and Lipscomb, T. H.: *Am. J. Physiol.* **90**:454, 1929.

13. Montgomery, M. L.: *Effect of Therapeutic Venous Ligation on Blood Flow in Cases of Arterial Occlusion*, *Proc. Soc. Exper. Biol. & Med.* **27**:178, 1929.

14. Montgomery, M. L., and Lipscomb, T. H.: *A New Continuous Volume Flow Apparatus (Modified Ludwig-Stolnikow Stromuhr)*, to be published.

RESULTS

Series 1.—(Carotid arterial, superficial femoral arterial and superficial femoral venous blood pressures and volume flow of blood through the iliac artery were recorded). The following protocol is representative of this group:

The animal was a short-haired, male dog weighing 12.5 Kg. Sodium barbital, 3.75 Gm. or 0.3 Gm. per kilogram, was given by stomach tube. After free dissection of the superficial femoral artery and vein, the iliac artery and the iliac and common iliac veins, and the carotid artery on the right side, and the inferior vena cava at its origin, the animal was left alone for thirty minutes. Then 0.375 Gm. of heparin, dissolved in 15 cc. of distilled water, was injected intravenously, and T cannulas

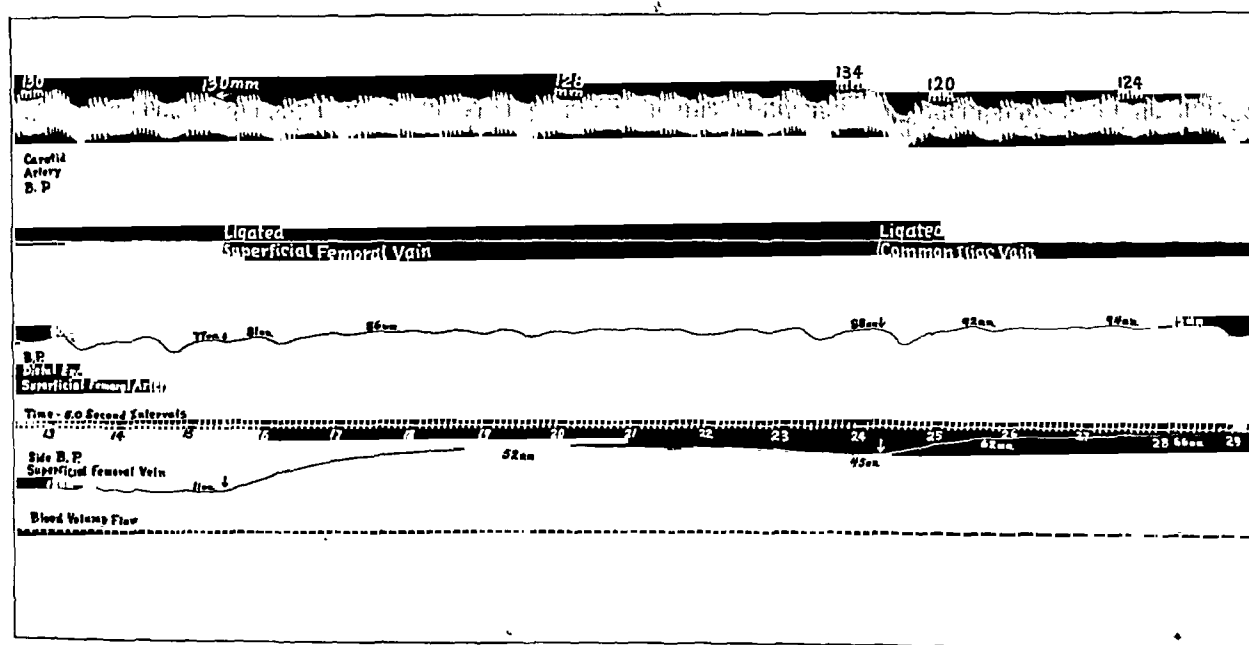


Chart 1.—Tracing showing the direct measurement of blood flow through the hind leg of a dog after ligation of the superficial femoral artery and subsequent "therapeutic" ligation of the superficial femoral vein and later of the common iliac vein. Ligation of the common iliac vein produced a marked decrease in the flow of blood through the leg.

were placed in the superficial femoral vessels and connected with mercury blood pressure manometers. The volume flow instrument was connected with the right iliac artery. The control flow through the iliac artery leveled off at about 40 cc. per minute. At this time the various blood pressures were as follows: carotid arterial, from 134 to 138 mm. of mercury; femoral arterial, from 118 to 126 mm. of mercury, and femoral venous, 16 mm. of mercury. Then the superficial femoral artery was ligated proximal to the T cannula and the flow of blood through the iliac artery fell abruptly to 29 cc. per minute, and later fluctuated between 31 and 36 cc. per minute. At the same time the femoral venous pressure leveled off at from 11 to 12 mm. of mercury and the femoral arterial at 80 mm. of mercury. After the flow had continued at this level for eight minutes, the superficial femoral vein was ligated. This caused the pressure in the superficial femoral artery and

vein to rise (chart 1). The former went from 77 mm. to 86 mm. of mercury and later reached 88 mm. of mercury. The latter rose from 11 mm. to 52 mm. of mercury and finally fell back to 45 mm. For a nine minute period the flow continued unchanged at a rate between 31 and 35 cc. per minute. When the common iliac vein was ligated, the rate fell sharply to 12.5 cc. per minute and finally leveled off at from 12 to 16 cc. per minute. At the same time the femoral arterial and venous pressures rose further, the former going from 83 to 92 mm. of mercury and the latter from 45 to 66 mm. of mercury. This rise occurred despite the fact that the systemic blood pressure, which had maintained a level of from 134 to 138 mm. of mercury, fell to from 120 to 124 mm. of mercury. Finally the inferior vena cava was ligated, and the flow fell sharply to 4.5 cc. per minute. This was accompanied by a fall in the systemic blood pressure to from 100 to 104 mm. of mercury, a slight fall in the superficial femoral arterial blood pressure to 88 mm. of mercury and a rise in the superficial femoral venous blood pressure to 72 mm. of mercury.

It should be stated that the high venous pressures developed in this experiment are not always seen. In the majority of cases, the rise is much less, but the comparative changes are otherwise similar in every way. In one such experiment, the venous pressure rose from a normal of 4 mm. to 20 mm. of mercury after ligation of the superficial femoral vein, and to 32 mm. after ligation of the common iliac vein.

Series 2.—(Carotid arterial blood pressure and volume flow of blood through the iliac artery were recorded.) The following protocol is representative of this group:

A long-haired, male dog, weighing 22.8 Kg., was used. Sodium barbital anesthesia was obtained with an initial dose of 2.6 Gm. injected intravenously, followed thirty minutes later by 1 Gm. intravenously. The animal was even then under light anesthesia as reflected in the respiratory fluctuations of blood pressure and blood flow, during deep respirations (fig. 2). These fluctuations were later controlled by small amounts of ether. The systemic blood pressure was taken from the left carotid artery. The right superficial femoral artery and vein were exposed only enough to permit ligation. The iliac artery was exposed freely as were the iliac and common iliac veins. The inferior epigastric artery and vein were ligated, to eliminate the drain of blood away from the extremity, and the animal was then left for fifteen minutes to aid coagulation of the small, invisible bleeding points. Then 0.68 Gm. of heparin, dissolved in 15 cc. of distilled water, was injected intravenously, and the volume flow instrument was connected with the right iliac artery. Ten minutes was required to make this connection, and in order to correct for reactive hyperemia the blood was allowed to flow through the instrument for a like period before the control record was taken.

Sharp fluctuations in the systemic blood pressure accompanied the deep respiratory movements and were associated with transient but marked changes in the rate of blood flow. As will be seen, however, the respiratory effects did not change the general trend. The control period flow of blood ranged between 123 and 130 cc. per minute for a ten minute period. Then the superficial femoral artery was ligated, and the flow fell rather quickly to 72 cc. per minute, after which it ranged between 70 and 80 cc. per minute for ten minutes. During this time the carotid arterial blood pressure fluctuated between 140 and 144 mm. of mercury. Ligation of the superficial femoral vein was now carried out and the rate of flow recorded

for sixteen minutes. At first the rate was unchanged. Then there was a moderate fall to range between 65 and 68 cc. per minute. The carotid arterial blood pressure was unchanged. At the end of this time the ligature about the superficial femoral vein was released. There was no immediate change in the rate of blood flow or in the systemic blood pressure. After eight minutes, however, the rate had fallen to between 58 and 60 cc. per minute. This was accompanied by a fall in carotid arterial blood pressure to 136 mm. of mercury.

With the femoral vein open, the iliac vein was ligated. This caused a prompt fall in the carotid arterial blood pressure from 136 to 130 mm. of mercury, and a sharp decrease in the volume flow of blood to 40 cc. per minute. This rate remained fairly constant for seventeen minutes. Then ligation of the common iliac vein reduced the blood flow to between 30 and 35 cc. per minute and the blood pressure to between 120 and 124 mm. of mercury.

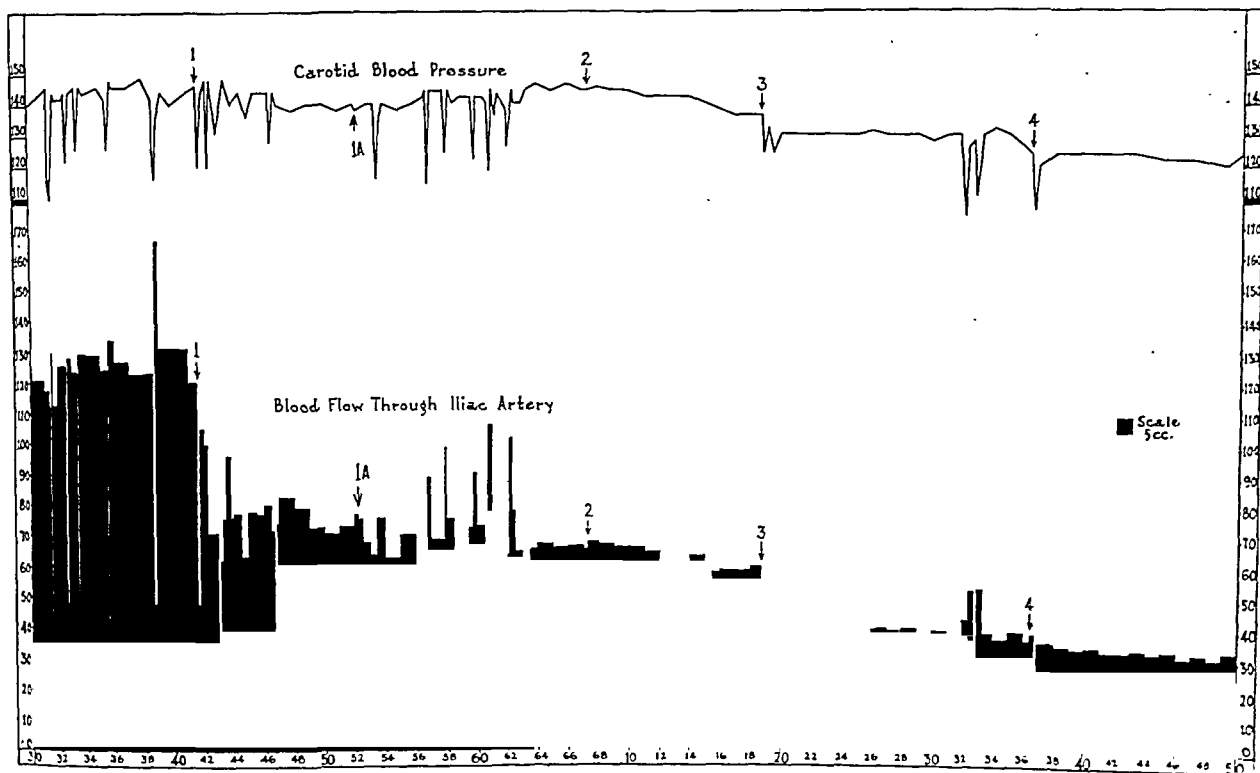


Chart 2.—Tracing showing the direct measurement of blood flow through the hind leg of a dog after ligation of the superficial femoral artery and subsequent "therapeutic" ligation of the superficial femoral vein, the iliac vein and finally the common iliac vein. The ligation of the latter two veins caused a decided reduction in the blood flow through the leg. 1 shows superficial femoral artery ligated; 1A, superficial femoral vein ligated; 2, ligature about superficial femoral vein released; 3, iliac vein ligated; 4, common iliac vein ligated.

SUMMARY

A fall in systemic blood pressure after ligation of the common iliac vein was observed in six of the ten experiments. The amount was quite variable. In four cases it ranged between 6 and 8 mm. of mercury. In two instances, with marked circulatory changes, it was much greater. Of the four other experiments there was observed a slight

transient fall in one, which rapidly returned to "normal"; in another there was no change; in the two remaining, the results were unsatisfactory.

The relationship between the fall in systemic blood pressure and the degree of decrease in the blood flow in our experiments is only a matter for speculation at present. Should a serious fall in blood pressure occur, it would, of course, affect the blood flow, but whether, with an otherwise adequate blood pressure, lesser changes of from 6 to 8 mm. of mercury exert an appreciable influence cannot be stated from the data at hand.

The superficial femoral vein was ligated in four experiments, and in each instance there was no increase in the flow of blood. The rate remained unchanged or decreased slightly during the eight to fifteen minutes of observation. In nine of the ten experiments, the common iliac vein was ligated, and in each instance there was an immediate, definite and at times pronounced fall in the per minute flow of blood. In the two experiments in which the inferior vena cava was ligated after ligation of the common iliac vein, there was a marked further decrease in the flow of blood which was associated with a rather sharp fall in the systemic blood pressure.

In each instance in which the vein was ligated, whether it was the superficial femoral, the iliac, the common iliac or the inferior vena cava, a rise occurred in the peripheral venous blood pressure. A similar rise was observed in the peripheral arterial pressure, except after ligation of the inferior vena cava, when, in one case, a slight fall was seen (see protocol, series 1). This fall seems to have occurred because the systemic pressure was closely approaching the level of the peripheral arterial pressure. In general, the peripheral blood pressures became higher with the more cephalad placing of the ligature.

When the common iliac vein was ligated permanently, dissection of the vascular bed after completion of the experiment showed the veins to be markedly distended with blood, in contrast with the collapsed, empty state of the veins of the opposite extremity.

COMMENT

It is evident from the results of these experiments that in the presence of acute obstruction of the superficial femoral artery in dogs, ligation of the superficial femoral vein, the iliac vein, the common iliac vein or the inferior vena cava does not increase the flow of blood to the extremity through the iliac artery. Indeed when, in these studies, any of the veins named were ligated, except only the superficial femoral, there occurred a definite decrease in the flow of blood so that as the position of the ligature became more cephalad the decrease became more pronounced. When the concomitant superficial femoral vein was ligated, the flow was either unchanged or decreased moderately. Whether ligation of the concomitant vein in other locations (as ligation of the iliac

artery and vein) has a similar or a different effect on the flow of blood to the part must await further experiments on a different species of animal, since the dog has no common iliac artery. The experiments of Brooks and Martin in which the common iliac vein was ligated after tying the iliac artery are, in fact, an application of the principle of proximal venous occlusion, and the decrease in blood flow which they postulated from the fall in temperature must be considered in that light.

The belief that ligation of the vein increases the flow of blood through the extremity must, therefore, be discarded, and the cause of such benefits as accrue from its use must be sought for elsewhere. The opinion of Brooks and Martin that ligation of the vein reestablishes the reduced peripheral blood pressure to a level above the minimum necessary to maintain a sufficient distribution of blood throughout the various capillary beds and to preserve the head of pressure required for the passage of nutrient elements from those capillaries into the surrounding tissues seems logical. Such benefits as occur are probably due to such a change.

On the other hand, as pointed out by these authors, the mere raising of the blood pressure is not sufficient. There must be a circulation of blood adequate for the basal conditions existing, and if ligation of the vein should produce a marked venous stasis, this stasis might be more menacing to final recovery than the reduction of pressure, especially if the latter was soon increased by the action of the collateral circulation. From such a stasis so-called ischemic paralysis might develop, with all of its attendant evils.

In addition, obstruction of the venous return may disturb the development of the collateral circulation as was proposed by Halsted.¹⁵ This author writes:

Since ligation of the vein raises the blood pressure in the ischemic area, is it not possible that the response of the arterial side for anastomotic development may be delayed or lessened for a period and to a degree conformable to the time and amount that the obstruction of the vein contributes to the maintenance of the circulation of the extremity? If this is so, might not the ligation of the like-named vein be postponed, when this can be done without danger, in order not to relieve the arterial side of its responsibility? Then if after a time there should be evidence of disability from ischemia, such as claudication on exercise, the surgeon would have the ideal opportunity to demonstrate the value of the venous ligation.

Halsted's conception is supported by the experiments of Theis, who found, on comparing ligation of the artery alone with ligation of the artery and vein (superficial femoral artery, common iliac vein), that, after the former procedure, the discharge of blood from the peripheral end of the ligated and divided femoral artery was at first smaller than, within an hour equal to, and three weeks later greater than after the latter procedure. This difference seems explainable only if it is assumed

15. Halsted, W. S.: Ligations of the Left Subclavian Artery in Its First Portion, *Johns Hopkins Hosp. Rep.* 21:1, 1921.

that there has been a better development of the collateral circulation to the femoral artery following ligation of the artery alone. Here again the principle of proximal venous occlusion has been used without clearly recognizing its import, as the author refers in his title to "Ligation of . . . Concomitant Vein" Whether ligation of the concomitant vein will show similar results remains undetermined. This work should be repeated and extended, as it has a fundamental bearing on the problem.

Recently the procedure has been brought into question further as the result of some experimental work on rabbits carried out in this laboratory by Wilson.¹⁶ In two series of experiments in each of which thirty animals were used, this worker ligated the iliac and common iliac arteries alone in one and ligated these arteries and the common iliac vein in the other. The incidence of gangrene was the same in both, 43 per cent. In addition, the functional results seemed to be somewhat more favorable after ligation of the artery alone, both as to the speed and as to the completeness of recovery.

Finally, a more careful analysis of the clinical reports leads one to feel that the procedure, as a method for general use, may have been received with too much favor. Makins' combined figures show, to be sure, a differential in favor of simultaneous ligation of the vein in the reduction of gangrene of 8.3 per cent (28 to 17.7 per cent). When the data are broken down into their component parts, however, it is found that there are great variations for the different parts of the body. The figures for the subclavian, axillary, brachial and carotid arteries seem overwhelmingly in favor of ligation of the vein. Nevertheless, the cases in which this procedure was carried out in each category are in reality too few to be of value in making significant deductions. On the other hand, for ligation of the femoral artery there was *no essential* difference between the two methods. The really promising results were found in the cases requiring ligation of the popliteal artery. Here the differential in favor of ligation of the vein was 20.2 per cent (41.6 to 21.4 per cent).

Sehrt's data, although favorable, are incapable of analysis and, for that reason, must be held in abeyance. Propping's two cases support the case for ligation of the vein when the carotid artery must be occluded.

Unfortunately Makins was unable to gather any important data on the final functional results in his cases. This is, after all, the real test of the method, and before its proper place in the surgery of the vascular system can be estimated, every effort must be made to study carefully and for a prolonged period of time each case that requires ligation of the healthy artery of an extremity, to the end that a larger clinical

16. Wilson, W. C., to be published.

material may be available for analysis. To this must be added a larger mass of experimental data analyzing carefully the effects of the various procedures on the vascular systems in the different parts of the body.

For the present, if the concomitant vein must be ligated, it appears that the ultimate prognosis will not be unfavorable in the majority of cases. If the popliteal artery has to be ligated, and the patient cannot be kept under careful observation, ligation of the concomitant vein should be practiced. If, however, the vein is intact and the patient is under careful observation, it may be well, as suggested by Halsted¹⁵ and Brooks,¹ to wait on the development of impending gangrene or symptoms of local circulatory insufficiency before resorting to ligation of the vein in any region. Then, if ligation seems desirable, it should be limited to the concomitant vein.

CONCLUSIONS

1. It has been shown in heparinized animals under sodium barbital anesthesia that after ligation of the superficial femoral artery:

(a) Ligation of the concomitant, superficial femoral vein causes no increase in the per minute volume flow of blood through the iliac artery, but causes either no change or a slight decrease, during the period of examination (from eight to fifteen minutes).

(b) Obstruction of the proximal venous return by ligation of the iliac vein, the common iliac vein or the inferior vena cava causes a pronounced decrease in the per minute volume flow of blood, the decrease being more marked the more cephalad the ligature is placed.

(c) In confirmation of the findings of Van Kend, Brooks and Martin and others, obstruction of the venous return increases the peripheral arterial and venous blood pressure and, in general, the increase is more marked the higher (more cephalad) the ligature is placed.

2. Because of the marked decrease in the flow of blood which follows obstruction of the venous return proximal to the point of arterial occlusion, and because of the possible danger of producing a serious venous stasis thereafter, it would appear that the use of this principle in the treatment of patients requiring ligation of the main artery of an extremity should be avoided.

3. The employment of ligation of the concomitant vein for occlusions of the injured, but otherwise healthy, popliteal artery is strongly supported by the clinical data. Its use in other locations is still a subject for debate and should await further experimental and clinical studies.

4. For the present, in the treatment of acute obstructions of the main arterial supply of an extremity, except the popliteal artery, in the absence of injury to the concomitant vein it seems wise to await the appearance of impending gangrene before resorting to ligation of the vein.

LATERAL CERVICAL TUMORS OF ABERRANT THYROID TISSUE

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Tumors arising in lateral aberrant thyroid tissue are not uncommon, and the literature pertaining to them was reviewed in 1901 by von Eiselsberg, in 1906 by Schrager and by Payr and Martina, in 1925 by Billings and Paul and by Fedeli, and in 1926 by Wegelin. The greatest number of case reports included in any single review is the fifty-three collected by Fedeli. Since there are at least one hundred and three published cases, to which we are adding six, we believe that a critical study of the entire group will be profitable.¹

It is probable that such tumors occur more commonly than the number of published cases would indicate. The anatomic origin of large invasive thyroid tumors is frequently difficult to determine, and it is likely that such tumors arising in aberrant thyroid tissue have in some instances been attributed to the thyroid gland. It is also probable that tumors of aberrant thyroid tissue have been mistaken for metastases of a benign tumor of the thyroid. The incidence in all cases of thyroid disease from which surgical specimens were obtained in Lakeside Hospital is slightly less than 0.1 per cent, which is in agreement with the figures published by Leech, Smith and Clute from the Lahey Clinic.

According to Gruber, the incidence of aberrant thyroid tissue in routine postmortem examination is over 10 per cent. If this figure is correct there should be about one-tenth as many malignant tumors of aberrant thyroid tissue as of the thyroid gland. There are, however, only thirty-one of the former reported, in contrast to over eleven hundred of the latter (Muller and Speese, Wilson, Graham, Simpson, Warren).

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1. Since the completion of this study nineteen additional cases of tumors of lateral aberrant thyroid tissue have come to our attention, which have not been included. Five were reported by Tebbutt and Woodhill, one by van den Wildenberg, four by Dunhill and nine by Cattell. The general characteristics of these tumors do not alter the conclusions reached in this study.

Several means of classifying tumors of aberrant thyroid tissue have been suggested. Wölfler divided them into two groups according to their apparent origin from either the medial or the lateral anlagen of the thyroid. Madelung, von Eiselsberg and Wegelin grouped them topographically as anterior, posterior, superior, inferior and lateral. Fedeli described two types, congenital and acquired. In our study it was found to be more convenient to recognize only two general groups, medial and lateral. The first group was adequately reviewed by Wegelin and includes those tumors that have developed along the course of the thyroglossal duct, together with those situated behind the trachea or esophagus. This study is concerned with the second group, the lateral cervical tumors of aberrant thyroid tissue.

One hundred and nine tumors arising from lateral aberrant thyroid tissue were classified as follows:

Adenomas	46 published case reports 2 studied by authors
Benign papilliferous tumors	20 published case reports 2 studied by authors
Malignant papilliferous tumors	20 published case reports 2 studied by authors
Carcinomas	9 published case reports
Miscellaneous (unclassified tumors)	8 published case reports

Total 109

In some instances the classification of these tumors was made irrespective of the diagnosis given by the author and is based on the descriptions and illustrations.

ADENOMAS (FORTY-EIGHT CASES)²

Included in this group were: (1) microfollicular, intermediate and macrofollicular adenomas; (2) cystadenomas; (3) cysts, and (4) collections of aberrant thyroid gland tissue, "tumors" only in the sense that a visible or palpable nodule not connected with the thyroid gland developed in the lateral cervical region.

In eleven instances the cystic change was so pronounced that the tumors were diagnosed cystadenomas. In the cases of multiple tumors in the same individual some were cystic while others were follicular (Reinbach, Pilliet, Madelung). That the cystic forms were degenerate adenomas is indicated by the tumors described by Demme and Fedeli.

2. Adenomas and cystadenomas of lateral aberrant thyroid tissue have been reported by Beerholdt, Busacchi, Cushway, D'Ajutolo, Demme, Deryuzhinski, Edmunds, von Eiselsberg, Fedeli, Haffter, Hinterstoisser, Jakoubovsky, le Jemtel, Lewisohn, Madelung, Martini, McGlannan, Patoureau, Payr and Martina, Pilliet, Pinner, Poland, Pollard, Rakhmaninoff, Reich, Reinbach, Rendu, Schrager, Schluter, Serenin, Socin, Ssalistchew, Stanley, Stern, Streckheisen, Tron and Zampa.

Although the diameters of the tumors varied between 1 and 10 cm. they were characteristically less than 5 cm. Encapsulation was constant, and frequent mention was made of the intimate adhesion of capsule to surrounding structures. In Streckheisen's case there were three lateral tumors, one of which was connected to the thyroid by a narrow strand of connective tissue. Association with lymphoid tissue was not common, an exception being a small submaxillary cystadenoma reported by Edmunds which was surrounded by lymphoid tissue. In cystic tumors, the contents were usually sanguineous, and in Schluter's case a single large cyst was aspirated repeatedly, brown fluid being withdrawn each time. In a woman, 24 years of age, there was periodic

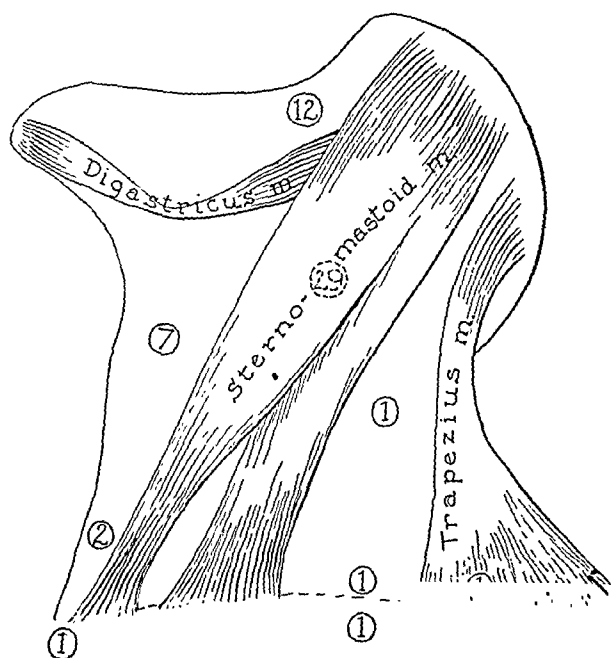


Fig. 1.—Diagram showing the distribution, in the neck, of adenomas, cystomas and cystadenomas of the lateral aberrant thyroid tissue.

swelling of the accessory tumors which suggested physiologic hypertrophy (Schrager).

The incidence of multiple tumors was the same as that of single tumors, there being twenty-two of each in which the protocols were explicit in that regard. The greatest number in one individual was eleven (Reinbach), while the average was three or four. In ten instances the tumors were on the right, in eight on the left and in five they were bilateral.

The distribution of tumors is indicated in figure 1. In twenty-nine cases the tumors were beneath the sternocleidomastoid muscle and frequently extended from under its anterior or posterior margin. Often the tumor nodules formed a chain which in some cases extended from occiput to clavicle. Although usually discrete, occasionally the tumors

were connected by fibrous strands, as described by Cushway. In seven cases the tumors were in the superior or inferior carotid triangle, and in twelve they were in the submaxillary triangle, in which situation they were most commonly below the angle of the mandible. Two were in the jugular notch, one was beneath the sternum, one was beneath the middle third of the clavicle, one was in the supraclavicular fossa, one was in the subclavian triangle and one was superficial to the trapezius muscle. The case reported by Busacchi illustrates how variable the distribution may be, there being one tumor in the superior carotid triangle, one in the jugular notch and one beneath the clavicular attachment of the sternocleidomastoid muscle.

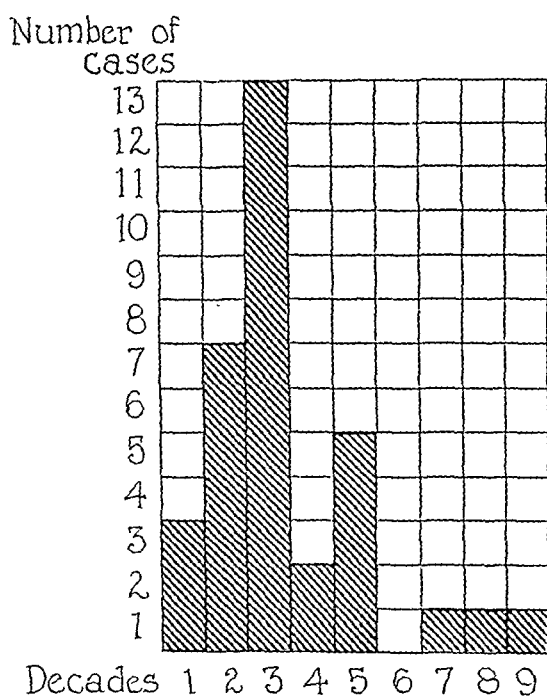


Fig. 2.—Chart illustrating the age incidence, by decades, of adenomas and cystadenomas of the lateral aberrant thyroid tissue, based on observation of the time of operation or autopsy.

The age at the time of operation or autopsy of persons having such tumors is shown in figure 2. The ages varied from the two cases of tumor occurring in infancy reported by Serenin to the case of an 84 year old woman reported by d'Ajutolo. In more than two thirds of the cases the patients were under 30, and since the average preoperative duration of the tumors, where such information was available, was fourteen years, it may be inferred that the lesion is essentially one of early life.

There was no direct relation between the duration and size of tumors; the largest tumor described (Schluter) developed in three

years and was cystic. Other large tumors reported by Poland, Madelung and Rendu were cystic, and it is probable that continued bleeding into a degenerate adenoma is the usual cause for rapid enlargement of a cystic tumor.

There was a striking contrast in the relative incidence in males and females. Of thirty-two cases in which the sex was given, five were males and twenty-seven were females. These were almost exclusively surgical cases and are comparable to a consecutive series of three hundred benign tumors of the thyroid received as surgical specimens in this laboratory in which the ratio of males to females was 1:4.

BENIGN PAPILLIFEROUS TUMORS (TWENTY-TWO CASES)³

Included in this group are: (1) tumors in which the papilliferous hyperplasia was primary and (2) tumors in which there was secondary papilliferous change in an otherwise adenomatous tumor. In most the papillae were macroscopic and sprang from the lining of cystic spaces. The cysts were unilocular or multilocular and were more or less completely filled by the papillae. The capsules were characteristically dense, fibrous and intact, and the tumors were frequently very irregular in shape with adhesions to adjacent structures. The papillae varied, some being delicate, branching structures, and others coarse, simple processes with rounded ends. Follicles were present either in the papillae or in solid portions of the tumor. Calcification, old and recent hemorrhage and lymphoid tissue were characteristically present. Lymphoid tissue was seen as an extracapsular zone as well as in the stroma of papillae. It was this characteristic of papilliferous tumors of the thyroid that led Langhans to suggest that they developed as an embryonal anomaly.

Eleven benign papilliferous tumors were multiple and ten were single. In the cases of Payr and Martina, McGlannan, Martini, and our case 4, several types of tumor, including solid or cystic nonpapilliferous forms, were present. Papillae were seen in adenomas, the seat of cystic degeneration, and as a secondary intrafollicular epithelial hyperplasia in solid adenomas. These tumors were larger than the simple adenomas, and the number of tumors described in individual cases was smaller. The largest tumors were reported by Leech, Smith and Clute (9 cm. in diameter), Pollard (7.5 cm. in diameter), and our case 4 (10 cm. in diameter).

The tumors in nine cases were on the right side, in five on the left and in one case bilateral. The distribution in the neck is shown in figure 3. In eight cases, tumors were found beneath the sternocleido-

3. Benign papilliferous tumors have been reported by Albrecht, Askanazy, Binney, Jores, Kapsammer, Leech, Smith and Clute, MacLennan, McGlannan, Martini, Payr and Martina, Pettersson, Plauth, Pollard, Reich, Reynier and Zahn.

mastoid muscle, in five in the submaxillary triangle, in seven in the superior and inferior carotid triangles, in one in the subclavian triangle and in four cases the tumors were described as supraclavicular.

The age incidence evinced no characteristic occurrence by decades and is shown in figure 4.

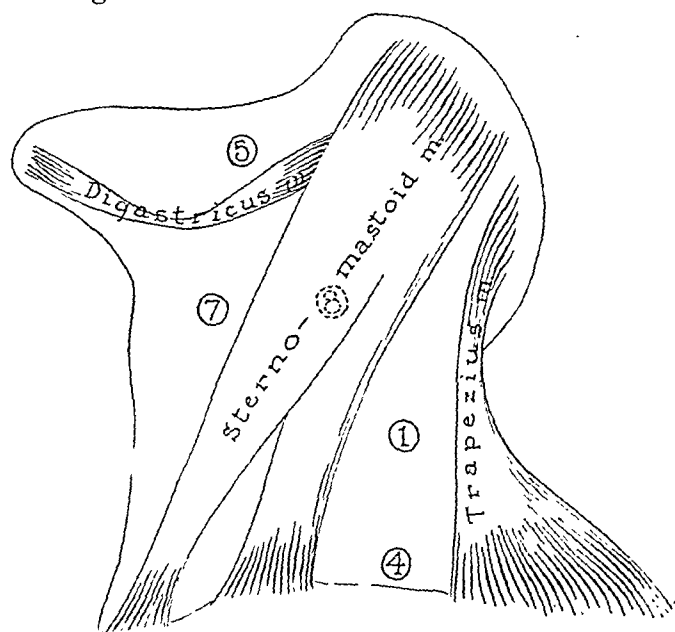


Fig. 3.—Diagram showing the distribution, in the neck, of benign papilliferous tumors of the lateral aberrant thyroid tissue.

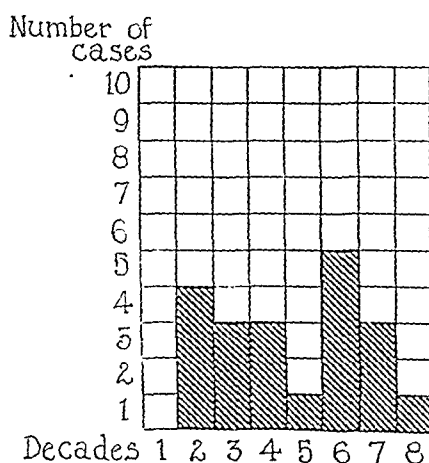


Fig. 4.—Chart illustrating the age incidence, by decades, of benign papilliferous tumors of the lateral aberrant thyroid tissue, based on observations at the time of operation or autopsy.

The preoperative duration varied, the longest being twenty-seven years (Reynier). Follow-up reports were too few to infer as to likelihood of recurrence. Nine of the patients were males and eleven were females.

PAPILLIFEROUS CARCINOMAS (TWENTY-TWO CASES)⁴

These tumors were similar to those of the preceding group, the essential difference being in their manifestation of invasive and metastatic extension. Transitional stages between the two groups were classified with difficulty, there being no characteristic structural differences between a tumor that was beginning to invade its capsule, a tumor that had extended through its capsule and a tumor that had metastasized to regional lymph nodes. In some, the descriptions would indicate that the papillae developed in a cystic adenoma (Barker; our cases 5 and 6), while in others the cystic character appeared to have followed continued intra-acinar proliferation in a macrofollicular adenoma (Kamsler, Fedeli). In eleven instances the tumors were multiple, and in ten they were single. In several cases (Barker, Billings and Paul, Fedeli, Wohl) in which the tumors were multiple, there was coexistence of adenomas, cystadenomas or benign papilliferous tumors, these frequently outnumbering the malignant tumors. Whether the malignant arose in benign tumors cannot be said with certainty. The malignant papilliferous character of a small part of some of the otherwise benign adenomas or cystomas as well as the coexistence of benign and malignant forms in one group of tumors suggested the evolution of malignant from benign tumors. In most instances the tumors were described as large with invasion of adjacent structures, and in ten of the twenty-two lymphatic metastases were recognized. Because of the common finding of lymphoid tissue in and around both the benign and malignant papilliferous tumors the recognition of metastases depended in some instances on the identification of tumor cells within lymphatics.

The distribution of the tumors is shown in figure 5 and does not differ greatly from the distribution of benign tumors (figs. 1 and 3). More than half of them were situated beneath the sternocleidomastoid muscles. There was no significant difference between the right and left sides of the neck and in three cases the tumors were bilateral (Leech, Smith and Clute, Lowe and our case 6).

Figure 6, showing the age incidence by decades, is modified by the long preoperative existence of the tumors. In six of eight cases in which there was a record of the appearance of the tumors, they had existed from nine (Barker) to twenty years (our case 6). Figure 6 indicates the ages of the patients at time of operation rather than the age incidence of the tumors. It can be said that at least seven of the twenty-one tumors were recognized in the first two decades of life. The long existence of tumors in persons who were operated on because

4. Malignant papillary tumors have been reported by Barker, Berger, Billings and Paul, Fedeli, Günzler, Hinterstoisser, Ignatyeff, Kamsler, Leech, Smith and Clute, Lowe, Payr, and Martina, Peyron, Ranque and Senez, Pool, Rühl, Schrager, Wegelin and Wohl.

of more rapid preoperative growth of the tumors lends added weight to the impression that the malignant change occurs in benign tumors. The number of cases followed was not sufficient to judge as to the likelihood of recurrence.

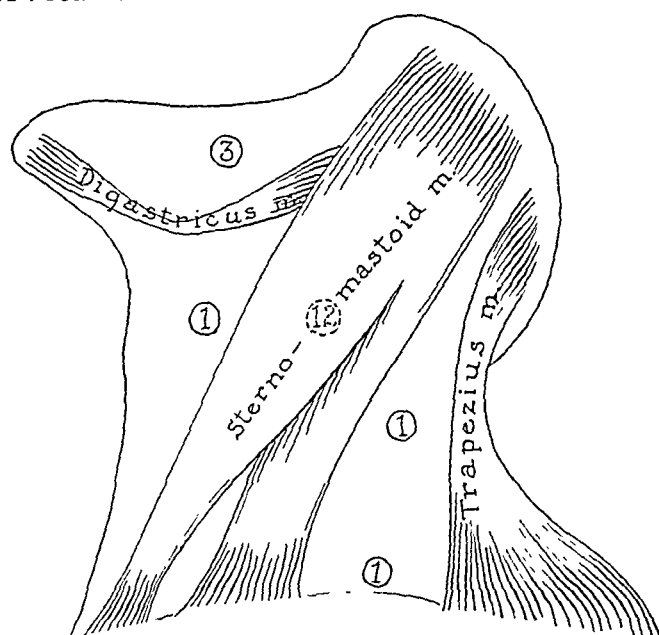


Fig. 5.—Diagram showing the distribution, in the neck, of papilliferous carcinomas of the lateral aberrant thyroid tissue.

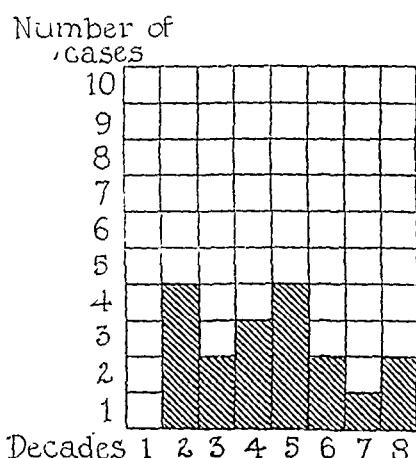


Fig. 6.—Chart illustrating the age incidence, by decades, of papilliferous carcinomas of the lateral aberrant thyroid tissue, based on observations at operation or autopsy.

CARCINOMAS (NINE CASES)

Nine nonpapilliferous carcinomas were found in the literature. They included four "adenocarcinomas" (Barnabó, Parcelier, Venot and Bonnin, Scharf, Greensfelder), one "alveolar carcinoma" (Hinterstoisser), and four "carcinomas" (Albert, Gutman, Nordman, Gerster). Most

of the tumors were described as large and in none of them was metastasis described. The group is too small to admit of comparative study. The ages of the patients at the time of operation varied from 18 (Nordman) to 65 (Barnabó). The preoperative duration and postoperative survival was not definitely stated in enough instances to be significant. Three of the tumors were in the submaxillary triangle, four were described simply as "lateral" and not connected to the thyroid, one was in the inferior carotid triangle and one was supraclavicular. Four were on the right side, two on the left and one (Parcelier, Venot and Bonnin) was bilateral. Seven of eight were in females.

MISCELLANEOUS (EIGHT TUMORS)

Eight tumors from the literature were not classified. Some had been diagnosed simply as tumors of lateral aberrant thyroid tissue but not described; others were placed in the miscellaneous group because of their pathologic description, although they were not so diagnosed in the case reports.

PATHOGENESIS

Several possibilities must be considered as to the pathogenesis of tumors of lateral aberrant thyroid tissue. Obviously conclusions as to pathogenesis are inferential and are based on probability. In this connection the value of the concept of the tripartite origin of the thyroid gland is important.

Although this question has long been controversial, three relatively recent investigations point to the participation of the ultimobranchial bodies in the development of the lateral lobes. According to Kingsbury, the descent and fusion of the ultimobranchial bodies with the median anlage is accomplished in embryos of from 12 to 15 mm. and since follicular differentiation is first seen in human embryos of 24 mm. (Norris) it seems probable that they do participate in the formation of the lateral lobes. Both Norris and Badertscher concur in this opinion, but the latter qualifies his conclusion in that "owing to the variable developmental behavior of the ultimobranchial bodies the relative proportion that they contribute to the thyroid varies." Variation in the development and descent of the ultimobranchial bodies or "lateral anlagen" presents one tenable theory as to the histogenesis of lateral aberrant thyroid tissue.

The abnormal development of the median anlage has served to account for the midline tumors of aberrant thyroid tissue (Wegelin) and cannot be excluded in a consideration of the development of lateral tumors. Although no comparison can be made between the thyroids of fishes and man, the migratory propensity of thyroid epithelium as

shown by Gaylord and March in salmonoid fishes suggests that even the more remote lateral cervical tumors might originate from the median anlage.

In regions of endemic goiter more or less completely detached nodules of gland tissue are seen frequently in nodular goiters. That such nodules could completely leave their parent connection may be possible as is suggested in cases reported by Rendu, Stern and Beerholdt. It seems improbable that they would migrate through fascial planes or into the posterior triangle.

Of the three pathogenic possibilities, no one appears correct to the exclusion of the other two. It is probable that all three serve to account for lateral aberrant thyroid tissue.

SUMMARY

Certain features pertaining to the entire group of tumors may be summarized as follows: The greatest incidence was in the third decade (fig. 7). Because the average preoperative existence of the tumors was eleven years (such information available in twenty-one cases), it can be said that they developed more commonly in early life and in this respect differed in age incidence from tumors of the thyroid. Benign tumors of the thyroid are seen in increasing numbers with advancing age (Wegelin), while Wilson found the highest incidence of malignant tumors of the thyroid to be in the fifth decade.

The ratio of males to females was 1:3, which was similar to the ratio observed in a series of surgical specimens of tumors of the thyroid gland. The tumors were situated on the right side more frequently than on the left, and in about 15 per cent of cases the tumors were bilateral.

The various types of tumor did not differ significantly in their location in the neck. The distribution is shown in figure 8. The most common site was beneath the sternocleidomastoid muscles. In a single case, however, tumors might be distributed widely in the neck, and their relation to fascia planes was not constant. Although the cases studied were selected as being tumors of true aberrant thyroid tissue, that is, not connected with the thyroid, in several instances of multiple tumors one of the tumors was connected to the thyroid by what was described as a fibrous strand.

More of the tumors were benign than malignant, and the coexistence of benign and malignant tumors was seen in six cases. The benign tumors did not differ essentially from those seen in the thyroid except for the relative frequency of papilliferous forms, a finding in almost 40 per cent of the total. The frequent occurrence of malignant papilliferous tumors was also striking, there being twenty-one papillifer-

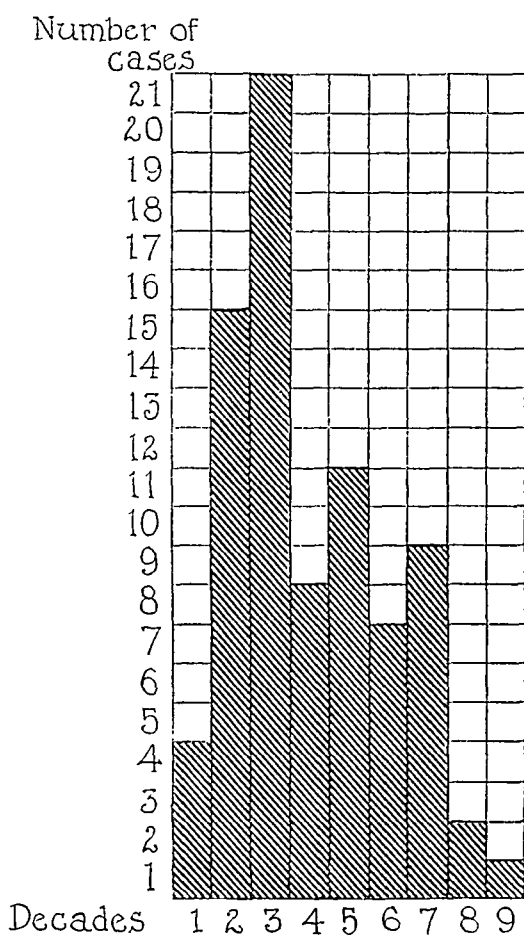


Fig. 7.—Chart illustrating the age incidence, by decades, of all tumors of the lateral aberrant thyroid tissue, based on observations at operation or autopsy.

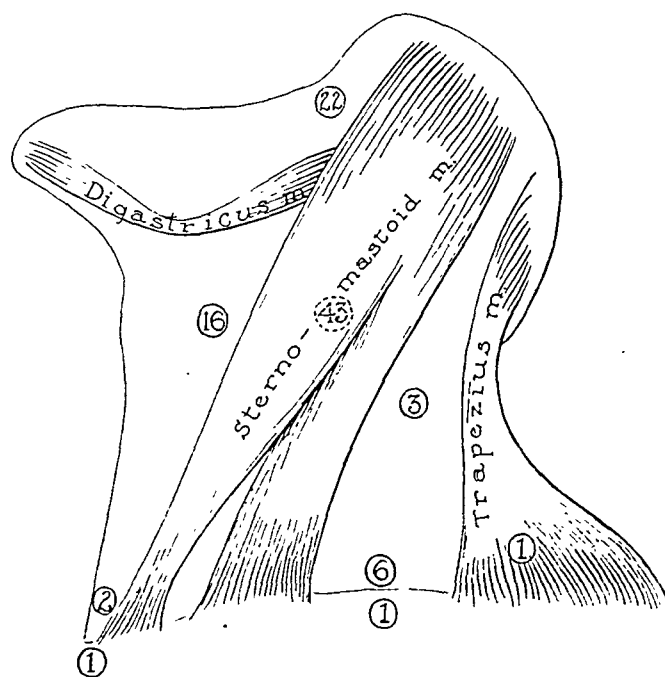


Fig. 8.—Diagram showing the distribution, in the neck, of all tumors of the lateral aberrant thyroid tissue.

ous to nine nonpapilliferous carcinomas, whereas the malignant papilliferous tumors of the thyroid constitute less than 10 per cent of the total (Moritz and Bayless).

REPORT OF CASES

CASE 1.—A white woman, 33 years of age, entered the accident ward and died in two hours of acute alcoholism complicated by morphine poisoning. At autopsy an encapsulated tumor mass measuring about 1 cm. in diameter was found lateral to, and above, the upper pole of the left lobe of the thyroid. There was no connection between this tumor and the thyroid. On section, the tumor was composed of macrofollicular colloid-containing adenomatous tissue which, microscopically, showed large follicles lined by flattened epithelium and filled with colloid. There was no evidence of lobular structure within the nodule and the capsule was intact. The thyroid gland was reported to be normal.

The diagnosis was macrofollicular adenoma of lateral aberrant thyroid tissue.

CASE 2.—A white man, 48 years of age, entered the hospital with an epithelioma of the right side of the mouth, present for eighteen months. Excision had been attempted prior to admission to hospital. Roentgen treatment was instituted, but was not judged to be effective. While the patient was in the hospital, several nodules in the right submental triangle and lateral cervical region were excised. One of them consisted of colloid-containing thyroid gland tissue. The thyroid itself was reported to be normal, and there was no connection between it and the aberrant thyroid tissue. The latter was encapsulated and contained an abundant amount of colloid. Microscopically, it consisted of large, fairly regular follicles lined by flattened epithelium and filled with uniformly staining colloid. No true lobular markings were noted although there was some pseudolobulation due to the irregular distribution of fibrous connective tissue.

The diagnosis was colloid adenoma of lateral aberrant thyroid tissue.

CASE 3.—A white man, 43 years of age, had a small tumor of unknown duration in the right supraclavicular fossa, which was found during a routine physical examination. The tumor, a cystic nodule, 1.5 cm. in diameter, was removed. The capsule was thick, fibrous and intact. Adhered to its outer surface was a narrow lamella of lymphoid tissue. On section, the cyst was seen to be almost completely filled by coarse, arborescent papillae, the ends of which were translucent and rounded. Microscopically, the epithelial cells covering the papillae were nonuniform, being columnar or cylindric in places and flattened in others. There was some formation of follicles on the surfaces of the papillae, and there were scattered rests of subcapsular, colloid-filled, resting follicles which were being encroached on by the hyperplastic papilliferous epithelium. The formation of papillae was not intra-acinar. There was focal calcification of capsule and papilliferous stroma, recent hemorrhage and intracellular hemosiderin deposition and diffuse lymphocytic infiltration. The contents of the cyst were sanguineous and included many desquamated cells.

The diagnosis was papilliferous cystadenoma of lateral aberrant thyroid tissue.

CASE 4.—A white woman, 56 years of age, presented two tumors of over three years' duration, behind the upper third of the left sternocleidomastoid muscle. One, measuring 10 cm. in diameter, was partially cystic and contained thick brown fluid. The cyst was indefinitely outlined, with a peripheral zone of colloid-containing adenomatous tissue which was for the most part macrofollicular. Microscopically, the follicles were the seat of intrafollicular papilliferous hyperplasia, the papillae being delicate and characteristically arborescent. Secondary acinar differentiation

was present in the papillae. Interspersed with the large follicles were collections of small, round, noncolloid-containing follicles. The capsule was intact. The other tumor measured 2 cm. in diameter and consisted of a thick-walled, smooth-lined cyst containing brown fluid. In both tumors there was evidence of old and recent hemorrhage, lymphoid infiltration and focal calcification.

The diagnosis was cystic papilliferous adenoma and cystadenoma of lateral aberrant thyroid tissue.

CASE 5.—A white woman, 62 years of age, had two tumors in the left supraclavicular fossa of about one year's duration. One was subcutaneous and the other was almost directly beneath it. They were not connected with each other nor with the thyroid gland. Both were removed. Each was globular and measured about 2 cm. in diameter. The capsule of the deeper tumor was invaded, with extension of tumor into underlying tissue. Both tumors were cystic. The capsule of the superficial tumor was intact, the contents were sanguineous, and the cyst was unilocular and partially filled by coarse, polypoid masses of papillae which grated on section. The deeper tumor also had a thick, though not intact capsule, was multilocular and completely filled by coarse, arborescent papillae. Histologically, the tumors were similar save for the extension of small atypical acini through the capsule and into the tissue adjacent to the deeper one. Papilliferous hyperplasia was present in these newly formed follicles, and as the center of the tumor was approached the follicles were larger and more completely filled by papillae. Papillae varied in size, amount of stroma, complexity and character of epithelium, the latter being pleomorphic with little acinar differentiation. Hemosiderin deposition and lymphocytic infiltration were prominent. There was a recurrence in four months.

The diagnosis was papilliferous cystadenoma and cystadenocarcinoma of lateral aberrant thyroid tissue.

CASE 6.—A white woman, 31 years of age, presented multiple, bilateral tumors, of about twenty years' duration, extending from occiput to clavicle beneath the sternocleidomastoid muscles. Tumors had been excised on three different occasions. Block dissection of the neck was performed in two stages. At the second operation one tumor, resting on the arch of the aorta, was not removed. The tumors varied from 1 to 3 cm. in diameter and most of them were encapsulated and globular. Some were simple smooth-lined cysts containing thin, colloid-like material, others were partially filled by coarse papillae, others were multilocular and were almost completely filled by papillae with extension of tumor into adjacent tissue, while still others were lymph nodes more or less completely filled by papilliferous and cystic tumor tissue. Histologically, the papillae were covered by cuboidal or columnar epithelial cells, many of which were swollen and piriform. Secondary follicular differentiation was not common. The invading margins of the tumor and the lymphatic metastases were characterized by intrafollicular papilliferous hyperplasia. Calcification and old and recent hemorrhage were common secondary changes. The calcium deposition was in the form of small calcospheres.

The diagnosis was multiple, bilateral cystadenomas, papilliferous cystadenomas and papilliferous cystadenocarcinomas of lateral aberrant thyroid tissue with metastasis to regional lymph nodes.

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INTRAVENOUS SODIUM AMYTAL AS AN ADJUNCT IN ANESTHESIA

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As the result of a preliminary study of the value of sodium amytal as an anesthetic in general surgery, I am of the opinion that its best field of usefulness is as a basal anesthetic administered intravenously. In this regard I am quite in accord with the views of Holman and Palmer¹ and others, and I now prefer to use comparatively small doses of the drug, supplementing it with some form of inhalation anesthetic, either nitrous oxide and oxygen or ether, preferably the former.

My experience with sodium amytal by mouth has been comparatively small, and no accurate comparison of the cases in which it was so given could be made with the present series. It has been my observation, however, that the results have been considerably less satisfactory and the effect less certain with such a method of administration. The intravenous route enables one to gage accurately the dose given; the effect is prompt and nearly constant, and it seems to me to be the preferable method for administration. In my total series of about 300 cases, there has been no evidence that such a technic is fraught with danger, and in none of the cases has any local reaction occurred even though a small quantity of the drug might accidentally have been spilled outside of the vein. The momentary discomfort of a venipuncture is slight if the injection is skilfully and carefully done.

As a study by Cabot, Maddock and Lamb had already been made of a series of 172 cases in which the so-called "full doses" of sodium amytal (from 15 to 25 mg. per kilogram of body weight) were given, it seemed desirable to analyze the records of a similar series in which the dose of sodium amytal was reduced to approximately one-half the amount given in the first group.

For the present study 129 cases were selected, taken quite at random, an effort being made to include as wide a variety of types of operations as was possible. In these 129 cases, there were 73 males, or 57 per cent,

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From the Department of Surgery, the University of Michigan.

The sodium amytal was furnished through the courtesy of Eli Lilly and Company, Indianapolis.

1. Holman, Emile, and Palmer, C. B.: Clinical Experiences with the Intravenous Injection of Sodium Isoamylethyl Barbiturate as an Auxiliary Anesthetic, *Am. J. Surg.* 9:55 (July) 1930.

and 56 females, or 43 per cent. The ages of the patients varied from 12 to 68 years, as shown in table 1, the average being 45.1 years.

Table 2 shows the various operations and the number of each performed.

METHOD OF ADMINISTRATION

For the most part, the patients were given preoperative medication consisting of morphine sulphate, from $\frac{1}{6}$ to $\frac{1}{4}$ grain (0.01 to 0.016

TABLE 1.—*Age Incidence*

Age by Decades	Number of Cases
1-9.....	0
10-19.....	14
20-29.....	21
30-39.....	24
40-49.....	30
50-59.....	23
60-69.....	17
	<hr/> 129

TABLE 2.—*Various Operations Performed in the Hundred and Twenty-Nine Cases*

Procedure	Number Performed	Procedure	Number Performed
Cholecystectomy	7	Posterior gastro-enterostomy.....	11
Thyroidectomy	27	Appendectomy	11
Cholecystostomy	2	Nephrectomy	5
Nephropexy	2	Nephrolithotomy	1
Resection of the cecum.....	1	Exploratory laparotomy.....	6
Enterostomy for an acute intestinal obstruction	2	Repair of a ventral hernia.....	4
Plastic operation on the face.....	5	Pylorectomy	1
Partial gastrectomy.....	6	Repair of multiple gunshot wounds of the intestine.....	1
Excision of a tumor of the breast	1	Secondary closure of the abdomen..	1
Hemorrhoidectomy	1	Cholecystogastrostomy	2
Colocostomy	1	Ureteral transplant	1
Splenectomy	1	Colostomy	5
Pylotomy	2	Inguinal herniorrhaphy.....	12
Resection of the colon.....	2	Combined abdominoperineal resection for cancer of the rectosigmoid	1
Spinal fusion	1	Incision and drainage of a subphrenic abscess.....	1
Excision of a malignant retained testis	1	Suture of lacerations of the face....	1
Open reduction fracture of both bones of the forearm (step-cut)....	1	Plastic operation on the arm.....	1
Incision and drainage of an abscess of the abdominal wall.....	1		
	<hr/> 64		<hr/> 65

Gm.), and atropine sulphate, $\frac{1}{150}$ grain (0.4 Gm.). In a few of the cases, no preoperative medication was used. It has been my feeling that atropine may be somewhat harmful in its effect by making the bronchial secretions thick and tenacious, thereby favoring postoperative atelectasis, and I have of late been using it much less extensively than formerly. The quality of anesthesia has been unquestionably better when morphine has been given before operation than when it has been omitted.

As the doses of sodium amytal employed have been so far below the accepted standard for maximum doses, the dosage for a given patient was not calculated beforehand according to body weight. Instead, a 10 per cent solution of the drug was made, the salt being dissolved in triply distilled water immediately before the injection was to be started. Great care was taken during the administration to give the drug slowly, the rate not exceeding 1 cc. per minute. The amount of the drug used was determined chiefly by its effect on the patient, a sufficient quantity being given to produce extreme drowsiness or complete hypnosis. This usually occurred when 5 or 6 cc. of the solution had been given, although patients vary considerably as to their tolerance. The elderly and debilitated respond much more promptly to the drug, whereas the young and robust tolerate a larger dose. Therefore, in those patients who were especially muscular and when the operation was to be a major one in the abdomen, particularly if it involved the upper quadrants, an additional 1 or 2 cc. was given after the patient was fully asleep. The smallest dose used was 2 cc., and the largest, 10 cc., the average for the entire series being 5.7 cc. The weight of the patients varied from 32 to 93 Kg., the average being 58.4 Kg. This means that an average dose of 9.8 mg. per kilogram of body weight was given.

During the administration of the drug, no excitement stage was noted, the patient dropping off quietly into a natural sleep without delirium or struggling. To nervous patients, and particularly in operations for toxic goiter, the sodium amytal was conveniently given in the ward without arousing suspicion on the part of the patient. This was usually done by the intern under the guise of a treatment, and a satisfactory "steal" could thus be carried out. The patient was thereby spared the fear and suspense of the trip to the operating room. Administration of the inhalation anesthetic was started just before the operation was begun. In all cases this was done before any attempt to start the operation, as the dose of sodium amytal was far short of one producing complete analgesia. The nitrous oxide-oxygen mixture was given in the usual manner. The mixture of the gases was in the ratio of 90:10 and this could ordinarily be considerably reduced after full surgical anesthesia was produced. In 2 or 3 cases in young and robust patients it seemed that the induction of gas was accompanied by a somewhat exaggerated excitement stage, although the quality of the anesthesia was not impaired after full surgical anesthesia had been obtained, and the performance of the operation was not hampered. In such cases, notably in young healthy adults, such as those so often seen for herniotomy or appendectomy, I have deemed it wise to increase the amount of sodium amytal to 15 or 20 mg. per kilogram. In this group of persons, there is not the objection to a period of somnolence lasting for several hours after operation that might be raised in the case of frail or elderly patients.

COMMENTS ON ANESTHESIA

In each case, before the patient left the operating room, the operating surgeon was asked to express his opinion regarding the quality of the anesthetic with reference to the facilitation of the operation. Table 3 shows the various opinions expressed.

Thus, in only 6 cases, or 4.7 per cent, was the anesthetic actually unsatisfactory, and in 97, or 75 per cent, it was entirely satisfactory, leaving a group of 26, or 20.3 per cent, in which it was considered to be fair.

On the whole, it was common experience to obtain considerably better muscular relaxation than with gas alone, but relaxation for abdominal work was necessarily less complete than that obtained with open ether or with spinal anesthesia.

While the nitrous oxide-oxygen induction was started with a 90:10 ratio of the two gases, this proportion of gas was usually rapidly decreased, so that a considerably lower percentage was employed during

TABLE 3.—*The Evaluation of the Anesthesia*

Result	Cases	Per Cent
Excellent.....	3	75.0
Good.....	60	
Satisfactory.....	34	
Fair.....	26	20.3
Poor.....	6	4.7
	<hr/> 129	

the major part of the operation. The actual percentage varied in different cases, the ratio of the two gases ranging from 93:7 to 50:50, the average for the series being 81:19.

By thus allowing the anesthetist to administer approximately twice the usual amount of oxygen in the mixture, much of the objectionable cyanosis so commonly attendant on nitrous oxide anesthesia was eliminated, and thereby a considerably greater margin of safety for the patient was made possible.

In 9 of the cases in the group it was necessary to reinforce the anesthetic by the addition of ether in some manner. In all but 1 case of this group this was done by means of ether vapor given through the McKesson machine. In 1 of the 9 cases it was necessary to change over to open ether. This operation involved excision of a large, retained, malignant testis, and it was the only one in which it was necessary to resort to open ether. The 9 cases in which the ether admixture was necessary were with one exception cases in which major operations were performed on the abdominal cavity, and the majority of these were operations on the stomach, as shown in the following enumeration: (1) posterior gastro-enterostomy and closure of an ulcer (acute perforation

of a duodenal ulcer); (2) Polya's resection of the stomach for a marginal ulcer; (3) thyroidectomy for a recurrent exophthalmic goiter; (4) enterostomy for an acute intestinal obstruction; (5) posterior gastro-enterostomy for a duodenal ulcer; (6) laparotomy for exploration of the biliary tract; (7) excision of a malignant, retained testis—open ether; (8) appendectomy for acute appendicitis; (9) posterior gastro-enterostomy for an advanced cancer of the pylorus.

The time interval required for the patient to react following operation is of interest. While several hours were always required for recovery when the larger doses of amytal were used, as in the earlier series, with the smaller doses as here advocated it did not seem that the time for recovery was delayed sufficiently to cause objection. While the sudden and immediate reaction from the anesthetic usually seen with gas was not present, the patient was recorded as having reacted "readily" in 75 of the cases. This meant that the patient would arouse when spoken to, but preferred to doze for a short time after the gas was discontinued. In 14 cases the reaction was recorded as "slowly," indicating that the patient had reacted in less than one hour. In the remaining 40 cases, the time of reaction was somewhat delayed, the longest time noted being six and one-half hours. The average reaction time for this delayed group was one hour and twenty minutes. The reaction was given readily in 75 cases, or 57 per cent; slowly, in 14 cases, or 11 per cent, and with delay, in 40 cases, or 31 per cent. With this comparatively short time required for recovery from the anesthetic, no difficulty was encountered in getting the patients to void or in the administration of fluids during the early postoperative period. Special nursing care was not deemed necessary unless the nature of the operation demanded it. In only 1 case was there any undue excitement period following operation, and this was in a patient with a very toxic exophthalmic goiter. It is doubtful whether the anesthetic was responsible in this case. It has not seemed that the amount of narcotics or sedatives required after operation was increased.

EFFECTS ON BLOOD PRESSURE

Of especial interest in the selection of any anesthetic is the effect it has on blood pressure. In the present study, the initial and final changes in pressure were carefully recorded. In each case a basal reading was taken before the administration of the anesthetic was begun. This basal systolic pressure varied from 84 to 230, the average for the series being 130. During the administration of the sodium amytal, the pressure readings were taken every minute. In 125 cases there was a fall in systolic pressure of greater or lesser degree. This initial fall varied from 2 to 124 mm. of mercury. In 1 case there was no initial

change, and in 3 cases there was an initial rise of 50, 14 and 42 mm. of mercury, respectively. In the cases showing a fall, the average fall was 30 mm. of mercury, or 23 per cent, and the total average initial blood pressure change was a drop of 29 mm. of mercury systolic pressure, or 22 per cent. The initial fall in pressure mentioned usually occurred rather promptly, the fall starting with the injection of the first cubic centimeter of the sodium amytal, and the maximum fall occurred shortly after the injection was completed, although in some cases the maximum drop did not occur until slightly later. Usually, with the beginning of the administration of the nitrous oxide, the pressure began to rise, so that it was practically back to normal at the conclusion of the operation. The readings of the systolic pressure at the end of the operation showed in 14 cases that the pressure was exactly the same as it had been in the beginning. In 54 cases it was below the recorded normal, and in 59 it was above the initial reading. The

TABLE 4.—Initial and Final Changes in the Blood Pressure

		Average	Total Average	Per-centage Average, Change per Cent	Total Average, Change per Cent
Initial Blood Pressure Change	Decrease 125 cases (96.9%)..	-30 mm. of Hg	-29 mm. of Hg	-23	-22.0
	Increase 3 cases (2.33%)....	+35 mm. of Hg		+27	
	No change 1 case (0.77%)...			
Final Blood Pressure Change	Decrease 55 cases (42.5%)...	-24 mm. of Hg	- 2 mm. of Hg	-17	- 1.5
	Increase 60 cases (46.5%)...	+18 mm. of Hg		+14	
	No change 14 cases (11.0%)			

average total change was a drop of 2 mm. of mercury. The average of the fall in those showing a final drop was -24 mm. of mercury, or 17 per cent. The average gain in the 59 cases showing a final rise was 18 mm. of mercury, or 14 per cent. In none of the cases was the fall in blood pressure sufficient at any time to necessitate restorative measures, such as the administration of ephedrine, epinephrine hydrochloride or dextrose intravenously. The moderate initial drop in blood pressure might serve at least as a theoretical argument against the employment of this drug in patients showing any degree of shock, and in none of the cases in this series has it been employed when shock was present even in a mild degree.

NAUSEA AND VOMITING

In 36 cases, or 28 per cent of the series, nausea and vomiting were present at some time during the postoperative period. In 10 of these it was confined to the few minutes immediately following the withdrawal of the nitrous oxide and during the period when the patient was being transferred from the operating table to the bed, with no vomiting after the return to the ward. In 18 cases there was slight vomiting after the

return to the ward, but this was at no time troublesome. In only 2 cases was vomiting at all prolonged or distressing, and in both of these it could be easily attributed to the operation itself rather than entirely to the anesthetic, as in both of these cases major operations on the stomach had been performed. In 6 cases there was occasional vomiting immediately after operation and for a short time after the return to bed. On the whole, such a tendency to nausea and vomiting shortly after operation was more apt to occur in the cases of goiter than in those of abdominal disorders, in all probability owing to the fact that a somewhat lighter grade of anesthesia was employed.

The findings presented in table 5 are substantially the same as I have observed with the use of nitrous oxide and oxygen without amytal or with ethylene, and I would conclude that the addition of the sodium amytal has practically no effect on the nausea and vomiting.

TABLE 5.—*Incidence of Nausea and Vomiting After Operation*

	Nausea and Vomiting	Number of Cases	Per-centage
Present		36	28.0
Absent		93	72.0
During first few minutes after operation; patient still in operating room		10	7.7
Occasional, after returning to ward.....		18	14.1
Both		6	4.7
Prolonged		2	1.5

PULMONARY COMPLICATIONS

One of the chief advantages that the nitrous oxide and oxygen anesthetic has always enjoyed over other inhalation anesthetics, ether in particular, has been the lower incidence of postoperative pulmonary complications. It has not seemed from the present study that the incidence of such complications was increased by the nitrous oxide-oxygen and amytal combination.

In 5 of the 129 cases, postoperative pulmonary complications were present, namely: bronchopneumonia in 2 cases; pleurisy with effusion in 1; transient pulmonary edema in 1, and mild bronchitis in 1.

One of the 2 cases of bronchopneumonia occurred in a man of 55 with a carcinoma of the head of the pancreas for which a cholecystogastrostomy was done. On the fifth postoperative day, a definite bronchopneumonia developed, as shown by clinical and roentgen examinations. He recovered satisfactorily. The other case occurred in a man of 45 with an advanced carcinoma of the cecum for which a resection was done. On the fourth postoperative day, bronchopneumonia developed, which along with a marked paralytic ileus proved to be fatal.

In the case showing pleurisy with effusion, the lesion was left-sided and occurred following splenectomy, coming on about one week after

the operation. The patient responded satisfactorily to treatment. As pleurisy with effusion is not infrequently found as a complication of splenectomy, it does not seem that it could be charged entirely to the anesthetic. There was 1 case of pulmonary edema that occurred after operation on a patient with an exceedingly toxic exophthalmic goiter. During the few stormy days immediately following operation, râles developed at the bases of the lungs. Roentgen examination of the chest failed to show definite evidence of pneumonia, and the condition rapidly subsided.

In 1 case, that of a young adult who had had an operation for the repair of an inguinal hernia, a mild bronchitis developed on the fifth day. This complication promptly cleared up, and did not delay the convalescence in any way.

Of the cases of pulmonary complications, it seems probable that only 4, i. e., 2 of bronchopneumonia, 1 of pulmonary edema and 1 of bronchitis, could be associated with the anesthetic. This makes a percentage of 3.1 per cent.

CONCLUSIONS

1. Sodium amytal administered intravenously is a valuable basal anesthetic for nitrous oxide-oxygen.

2. A better quality of anesthesia and more complete muscular relaxation can be obtained than with nitrous oxide and oxygen unassisted.

3. A considerably higher percentage of oxygen is possible than with gas alone, thus tending to decrease the objectionable cyanosis and making for a greater margin of safety.

4. The easy, quiet induction, along with the slow and gradual awakening, is appreciated by the patient.

5. In nervous patients, or in cases of toxic goiter, the anesthetic can easily be given in the patient's room without exciting suspicion, thus greatly facilitating the "steal" type of operation.

6. Postoperative nausea and vomiting are not greater than with nitrous oxide and oxygen unaided.

7. There is usually an initial fall in blood pressure amounting to 29 mm. of mercury, or 22 per cent, in this series, which might be regarded as a contraindication to its use in certain cases, e. g., shock.

8. When used as a basal anesthetic with gas, the incidence of pulmonary complications is not increased.

VARIATIONS IN PHOSPHATASE AND INORGANIC PHOSPHORUS IN SERUM DURING FRACTURE REPAIR

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AND

L. KRAEER FERGUSON, M.D.

PHILADELPHIA

A study of the phosphatase concentration of the blood during the union of fractures seemed to us of interest because of the evidence that is accumulating that phosphorus metabolism is one of the important factors in the deposition of bone salts. Robison¹ has shown that phosphatase, an enzyme extracted from bone and ossifying cartilage and in smaller quantities from other tissues, can liberate inorganic phosphorus by breaking down solutions of complex organic compounds of phosphorus, such as glycerophosphates and hexosephosphates. Calcification has been observed of rachitic bone immersed in solutions of these two salts.² It is Robison's hypothesis that the phosphatase available in the cells of bone and ossifying cartilage reacts with glycerophosphates or hexosephosphates in the blood. By this means there is produced a local increase in inorganic phosphorus in the region of these cells. This increase in phosphorus alters the equilibrium between calcium and phosphorus ions in this area and results in the deposition of calcium phosphate. Ossification of this type therefore would require for its production in the animal body the presence both of the enzyme, phosphatase, and a substance from which it could liberate inorganic phosphorus, such as sodium glycerophosphate or sodium hexosephosphate. That the enzyme is present in bone and in the circulation was shown by Martland, Hansman and Robison,³ Demuth,⁴ Kay,⁵ Roberts⁶

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and Bodansky.⁷ The presence in the blood of the necessary type of organic phosphorus compounds, which may be broken down by phosphatase, was demonstrated by Kay and Robison⁸ and by Kay.⁹ Thus evidence has been presented by previous workers for the presence in the animal body of the two factors necessary for the type of calcium phosphate precipitation observed *in vitro* by Robison. If a mechanism of this type were active during repair of fractures, an increase in phosphatase of the blood might be expected as a result of the increased activity of the bone cells at the site of fracture. This in turn might be related to the increase in inorganic phosphorus which is known to occur.¹⁰

The results of a study of the phosphatase activity of the blood during the union of fractures are presented in the present paper, together with an apparent relation between the enzyme and the inorganic phosphorus of the blood. We have been able also to confirm the findings of Kay¹¹ and Roberts⁶ with respect to the increase in phosphatase in the blood in generalized disease of bone.

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11. Kay, H. D.: Plasma Phosphatase: II. The Enzyme in Disease, Particularly in Bone Disease, *J. Biol. Chem.* **89**:249, 1930. Footnote 5.

METHOD

The phosphatase activity of the blood is determined as the amount of inorganic phosphorus liberated during incubation from a solution of an ester of phosphoric acid, such as sodium glycerophosphate, by the action of the enzyme present in whole blood, serum or plasma. From the inorganic phosphorus content of the reaction mixture after incubation is subtracted the inorganic phosphorus originally present in the 1 cc. of serum used for the test. The difference in these two values then represents the inorganic phosphorus liberated by the action of the enzyme, since no increase in phosphorus over the control value is produced in sodium glycerophosphate incubated without serum or in serum incubated without glycerophosphate.

In the method devised by Kay,⁵ centrifugated plasma was used, after filtration through cotton to remove leukocytes, which are known to contain phosphatase. We have used centrifugated serum without filtration and found that clot formation apparently was effective in immobilizing leukocytes, since none could be demonstrated in stained spreads of the serum after centrifugation. Instead of the two tubes of saline solution as controls used by Kay, we have used one tube containing serum and substrate, identical with those that are incubated, in which the phosphorus is determined immediately after adding the substrate to the serum. Controls of this type have agreed well with the saline-substrate tubes. This elimination of one control tube and of the filtration through cotton with consequent small loss of material make it possible to draw less blood for the test, which is desirable if successive determinations are to be made on the same patient.

Determinations of p_H indicated that there was no change in the reaction of the mixture of serum and substrate after incubation for forty-eight hours at 38 C. The p_H of the solution was in all cases 7.85 ± 0.05 , determined with phenol red at 38 C. Our hydrolysis values are not therefore directly comparable with those of Kay, which are corrected to p_H 7.6, but are about 25 per cent higher. Samples of authentic sodium beta-glycerophosphate, recommended by Kay as a substrate, were not available at the time this work was started, and we therefore used commercial preparations of sodium glycerophosphate (Powers, Weightman, Rosengarten Company, Eastman Kodak Company, no. 644). These were found to have but a minimal content of the contaminating alpha-glycerophosphate, as shown by Grimbert and Bailly's¹² application of the reaction of Deniges. Kay¹³ recently reported a method for the differentiation of the alpha and beta isomers of glycerophosphoric acid and also found that the Eastman salt is principally the beta-glycerophosphate. Differences in concentration of substrate (0.15 and 0.25 per cent) produced no variation in hydrolysis.

Sodium glycerophosphate was used as a substrate. The salt should be assayed¹⁴ for its content of anhydrous sodium glycerophosphate, and the solution made so that 4 cc. will be equivalent to 1 mg. phosphorus. This is a correction of small magnitude in these two salts, and the corrected strength will be close to the theoretical strength of 0.254 per cent.

12. Grimbert, L., and Bailly, O.: Sur un procédé de diagnose des monoethers glycerophosphoriques et sur la constitution du glycerophosphate de sodium cristallisé, *Compt. rend. Acad. d. sc.* **160**:207, 1915.

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Three cubic centimeters of serum are required. Centrifugate the blood as soon as possible for five minutes at high speed (approximately 3,000 revolutions per minute). Withdraw the serum carefully in one operation, and transfer to small test tube.

Measure 1 cc. of serum into each of three test tubes, 15 by 100 mm. To two of these tubes add 4 cc. substrate and 1 drop of chloroform. Stopper well and put in the incubator at 38 C. for forty-eight hours. To the 1 cc. of serum contained in the third, or control, tube also add 4 cc. substrate and 1 drop of chloroform. Mix well and immediately withdraw 4 cc., which is added to 4 cc. of trichloroacetic

TABLE 1.—*Inorganic Phosphorus and Phosphatase Activity in Serum in Cases of Fracture*

Date	Patient	Age, Years	Days Since Fracture	Degree of Trauma	Inorganic Phosphorus, Mg. per Cent	Phosphatase Activity, Mg. Phosphorus	Fracture
8/ 6/30	F. C.	14	162	+++	4.3	0.59	Intracapsular fracture of femur
8/28/30	F. B.	21	14	++	4.6	0.45	Outer and middle third of clavicle
8/29/30	J. K.	21	6	++	5.6	0.29	Epiphyseal separation of radius
9/ 4/30	O. V.	7	3	++	4.8	0.40	Outer and middle third of clavicle
9/ 9/30	H. B.	30	12	+++	5.4	0.33	Distal phalanx of great toe
9/30/30	G. M.	15	6	+	5.3	0.45	Epiphyseal separation of head of radius
10/ 2/30	J. S.	16	2	+++	5.4	0.68	Epiphyseal separation of lower end of humerus
10/21/30	A. M.	12	2	++	4.7	0.70	Epiphyseal separation of middle phalanx of fifth finger
11/11/30	H. T.	17	1	+++	4.8	0.68	Radius and ulna
12/ 9/30	K. E.	51	15	++	3.8	0.35	Comminuted fracture of lower end of radius
1/27/31	J. N.	60	3	++	5.9	0.19	Neck of femur
4/11/31	H. L.	45	180	++++	5.5	0.57	Nonunion of femur
Average.....					5.0	0.47	

acid, 10 per cent, contained in a 50 cc. Erlenmeyer flask. Shake well, filter off the precipitated protein through filter paper, and determine the inorganic phosphorus in 4 cc. of the filtrate.¹⁵ The control value thus obtained is subsequently subtracted from the inorganic phosphorus found in the two incubated tubes. The phosphorus liberated by the enzyme in these tubes is determined in 4 cc. of the trichloroacetic acid filtrate prepared as in the control. The activity of the enzyme is reported in terms of milligrams of phosphorus liberated from 4 cc. of the substrate by 1 cc. of serum. Since the 4 cc. of trichloroacetic acid filtrate used for the phosphorus determination is equivalent to 2 cc. of the serum-substrate mixture, the phosphorus present in the total 5 cc. of this mixture is obtained by multiplying by 2.5 the phosphorus found in the 4 cc. of the filtrate.

15. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* 66:375, 1925.

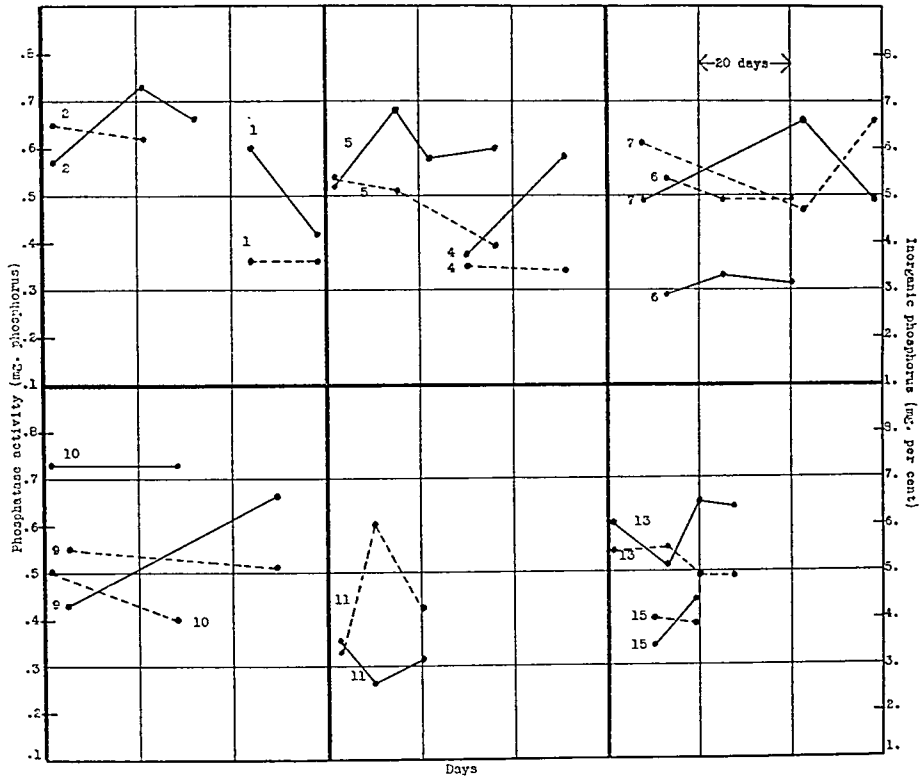


Fig. 1.—Phosphatase activity of serum during union of fractures compared with inorganic phosphorus of serum. Solid lines indicate phosphatase activity. Broken lines indicate inorganic phosphorus. Time since fracture is measured from the left margin of each oblong area.

TABLE 2.—Phosphatase Activity of Serum During Union of Fractures Compared With Inorganic Phosphorus of Serum

Curve	Age of Patient	Degree of Trauma	Fracture
1	11	++++	Tibia and fibula
2	4	++	Clavicle
4	37	+	Middle metacarpal
5	14	+	Incomplete, lower end of fibula
6	22	++	Radius and ulnar styloid
7	13	++++	Radius and ulna
9	12	++	Tip of ulnar styloid, epiphyseal separation of radius
10	14	++	Clavicle
11	19	++	Clavicle
13	12	+++	Radius and ulna
15	21	++++	Head of radius and olecranon process

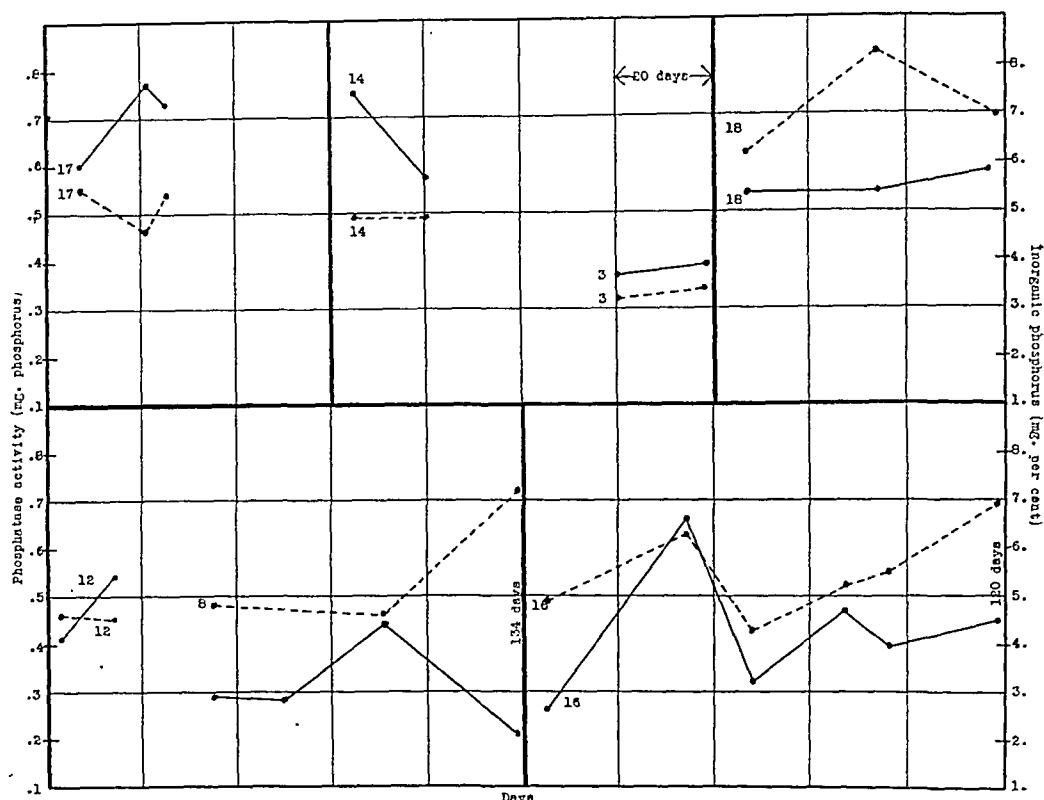


Fig. 2.—Phosphatase activity of serum during union of fractures compared with inorganic phosphorus of serum. Solid lines indicate phosphatase activity. Broken lines indicate inorganic phosphorus. Time since fracture is measured from the left margin of each oblong area.

TABLE 3.—Phosphatase Activity of Serum During Union of Fractures Compared With Inorganic Phosphorus of Serum

Curve	Age of Patient	Degree of Trauma	Fracture
3	26	+++	Tibia and fibula
8	64	+	Radius
12	13	++	Radius
14	50	++	Radius, comminuted
16	31	++++	Femur
17	12	+	Olecranon process of ulna
18	12	++++	Femur

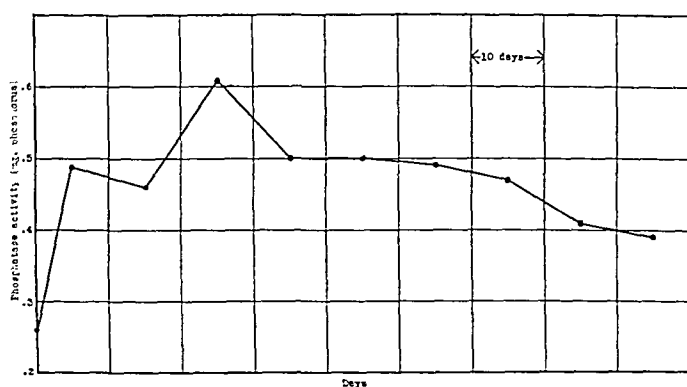


Fig. 3.—Composite curve of phosphatase activity in ten day periods following fracture from cases in tables 1, 2 and 3.

TABLE 4.—*Inorganic Phosphorus and Phosphatase Activity in Serum in Patients With Bone Disease*

Patient	Age, Years	Date	Inorganic Phos- phorus, Mg. per Cent	Phos- phatase Activity, Mg. Phos- phorus	Diagnosis
G. W.	6 mo.	4/ 8/30	9.0	0.56	Rickets
W. H.	79	4/ 8/30	7.0	0.56	Cancer of prostate, with bone metastases
H. P.	32	7/31/30	4.4	0.21	Giant cell sarcoma
F. C.	39	9/ 9/30	5.4	0.65	Osteomyelitis following compound fracture
W. C.	22	9/17/30	6.4	0.53	Recurrent osteomyelitis
S. L.	50	10/ 7/30	5.6	0.68	Paget's disease
C. Q.	40	10/22/30	5.1	0.73	Paget's disease
J. M.	44	11/10/30	4.5	0.50	Osteochondroma of hip
J. P.	22	11/14/30	3.8	0.46	Bone cyst
V. L.	9	11/21/30	5.5	0.69	Rarefaction of fibula
A. L.	60	10/21/30	4.3	0.73	Paget's disease and carbuncle
		11/10/30	3.7	0.76	
J. G.	..	12/ 1/30	4.8	0.60	Cancer of prostate, with bone metastasis
		12/11/30	4.3	0.61	
H. G.	60	11/26/30	4.9	0.45	Cancer of prostate, with bone metastasis
		12/11/30	3.5	0.34	
H. P.	63	12/ 1/30	4.8	0.35	Cancer of prostate, with bone metastasis
		12/11/30	3.8	0.33	
W. M.	22	2/27/31	7.9	0.46	Old osteomyelitis, with acute recurrence
		3/ 4/31	6.5	0.51	
Average.....			5.3	0.54	

TABLE 5.—*Inorganic Phosphorus and Phosphatase Activity in Serum in Patients Without Disease of Bone*

Patient	Age, Years	Date	Inorganic Phos- phorus, Mg. per Cent	Phos- phatase Activity, Mg. Phos- phorus	Diagnosis
J. W.	79	2/ 8/30	3.0	0.14	Myocarditis
J. G.	68	2/21/30	5.0	0.45	Polycythemia vera; white blood cells, 22,800; red blood cells, 6,340,000
E. R.	20	3/ 7/30	5.7	0.17	Typhoid fever
F. J.	58	3/31/30	5.0	0.23	Cardiorenal disease
A. F.	31	4/ 3/30	5.3	0.20	Dementia praecox
R. B.	26	4/ 4/30	6.0	0.24	Sickle cell anemia
F. S.	31	4/ 5/30	5.8	0.35	Myocardial degeneration; white blood cells, 40,000
O. C.	..	4/ 8/30	6.2	0.21	Chronic polyarthritis
J. S.	76	4/ 8/30	9.0	0.16	Cardiorenal disease
J. M.	59	4/15/30	5.0	0.20	Scurvy and myocarditis
J. B.	60	5/19/30	3.2	0.14	Intestinal obstruction
M. W.	33	6/17/30	2.3	0.20	Bromide poisoning
A. H.	20	9/ 4/30	3.8	0.20	Tumor of breast
W. H.	24	9/ 4/30	3.9	0.20	Foreign body in forearm
M. C.	30	9/ 4/30	4.3	0.16	Acute furuncle of thigh, two weeks' duration
M. R.	27	9/ 9/30	7.0	0.17	Burn on leg
J. G.	18	9/11/30	3.9	0.38	One month after furuncle of arm
R. J.	22	9/17/30	3.6	0.33	Chronic leg ulcer
J. B.	34	9/17/30	4.2	0.31	Subsided acute infection
C. E.	25	9/17/30	5.3	0.25	Slight contusion of head
M. S.	33	9/24/30	4.0	0.42	Inguinal hernia
P. F.	32	9/24/30	4.6	0.30	Chronic myositis trapezius
I. S.	60	9/30/30	5.3	0.34	Chronic sinus
J. T.	26	9/30/30	4.2	0.28	One week after stab wound
E. A.	49	10/ 1/30	4.9	0.23	Multiple furunculosis
A. H.	38	10/21/30	3.4	0.30	Ganglion on wrist
E. E.	30	12/31/30	4.3	0.33	Cyst on ear
J. S.	..	2/11/31	7.1	0.18	Chronic arthritis
W. L.	31	2/27/31	6.5	0.27	Herniorrhaphy
D. K.	30	3/23/31	4.6	0.31	Hemorrhagic retinitis
Average.....				0.26	

COMMENT

Single determinations of phosphatase were made in twelve fracture cases (table 1) and serial determinations in eighteen (charts 1 and 2 and tables 2 and 3). Most of the patients were ambulatory, treated in the fracture clinic of the surgical outpatient department of the University of Pennsylvania Hospital. Determinations in several cases of fractures of large bones were made on patients in the surgical wards of the Philadelphia General Hospital. The phosphatase values in nearly all of these fracture cases and in the fifteen cases of other types of bone involvement studied (table 4) showed greater activity than that in thirty patients presenting no involvement of the bone (table 5).¹⁶ The average value in the cases of table 5, without such involvement, is 0.26 mg. The average of the entire fracture series is 0.49 mg. and that of the other types of bone involvement 0.54 mg. From the serial studies shown in charts 1 and 2 it may be seen that at varying intervals after fracture there is an increase in the phosphatase activity, with a slow return to normal as union progresses. This is most apparent in the composite curve of chart 3, which is composed of the average values for ten day periods of the fracture series. It was impossible to follow the cases as completely as would have been desirable, so that in some curves no complete cycle of increase and decrease was obtained, but from the form of the composite curve we believe that in cases 1 and 14, for example, specimens obtained earlier in the course of union would have shown the rising value. In other cases, such as 9, 12 and 15, it was impossible to obtain blood late enough to indicate whether the decrease would appear as union became complete. The increase in cases 6 and 18 is too small to be significant, and the decrease in case 11 and the continued high level in case 10 remain unexplained. Individual variation in the mechanism of fracture repair and unrevealed differences in the extent of bone damage may both play a part in accounting for the lack of a uniform response in all the cases. Diet also is a factor that may cause variation, as the increase found in case 8 followed correction of the patient's habitual diet to include milk, eggs and green vegetables. The other cases show the increase to a maximum and subsequent gradual decline, which we believe to be the normal cycle. Correlation of the phosphatase activity with the degree of soft tissue trauma gave no concordant results.

It is not clear whether the additional enzyme in the blood during union is liberated from damaged bone or soft tissue, as Murray¹⁷ has

16. The figures for inorganic phosphorus in table 5 are not to be considered as values found in normal subjects. The subjects were all undergoing treatment and their phosphatase activities were used for comparison only because they were free from bone lesions, as nearly as could be determined.

17. Murray, C. R.: Delayed and Non-Union in Fractures in the Adult, *Ann. Surg.* 93:961, 1931.

suggested, or whether the increase follows increased activity of the bone cells during the repair process. If the source is neither in damaged tissue nor hyperplastic bone cells, the increase may represent mobilization of the enzyme from other depots, such as the intestinal wall or kidney, since the enzyme occurs, but in lower concentration, in tissues other than bone.

From the form of the composite curve of phosphatase values in chart 3, which is similar to curves of inorganic phosphorus obtained by other investigators in fracture cases, one would expect that individual curves of phosphatase and inorganic phosphorus would be parallel. However, comparison of our figures gave somewhat surprising results. In eight of our cases there appeared to be an inverse relation between these two substances, a decreasing phosphorus being associated with a rising phosphatase, and vice versa. The phosphorus values were principally in the region of 5 mg. per hundred cubic centimeters, the value reported by Tisdall and Harris¹⁸ as the level in the blood during fracture repair, but we found variations above and below this level. Serial determinations of inorganic phosphorus during fracture repair, such as those reported by Bellelli,¹⁹ indicate that marked fluctuations may occur. We have no information at this time that would indicate whether the change in inorganic phosphorus is the cause or the effect of the change in phosphatase, or whether, indeed, any relation other than a fortuitous one exists.

A study of experimental fractures in dogs in order to secure further information on the variation in serum phosphatase and its possible relation to changes in inorganic phosphorus has thus far given inconclusive results.

SUMMARY

1. An increase in phosphatase has been observed in the serum of patients with fracture on whom serial determinations were made.
2. A trend toward an inverse relation has been noted between the concentrations of phosphatase and those of inorganic phosphorus.
3. This increase in phosphatase is thought to be significant as a factor in the repair of fractures.
4. Increased concentration of the enzyme in serum in generalized disease of bone has been observed, confirming the studies of previous workers.

18. Tisdall and Harris (footnote 10, first reference).

19. Bellelli (footnote 10, eighth reference).

SACROCOCCYGEAL CHORDOMA

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HALSTEAD, KAN.

In 1926, Stewart and Morin reported a case of sacrococcygeal chordoma and published a complete bibliography up to that date. They reviewed fifty-seven cases of all varieties previously reported. Since that time the number of cases of chordoma reported has reached something over eighty. In this paper I wish to add another proved case and to record the literature that has appeared since Stewart and Morin's article.

REPORT OF A CASE

History.—J. W., a man, aged 53, a farmer, entered the hospital on Nov. 23, 1930, complaining of an ache in the region of the coccyx. Eighteen months previously, after riding a tractor over rough ground, a soreness developed in the coccygeal region, and on examination he felt a small lump. He supposed it to be a swelling due to trauma.

The lump persisted and slowly grew larger. It caused no symptoms at that time. Two months prior to admission he noticed a dull ache in the region of the coccyx, which was felt more while sitting than standing. There was never any sharp or severe pain. Two days before entering the hospital he was aware of an ache in the region of the right hip joint and extending down the back of the thigh. He had been constipated for a long time, but there never had been any interference with defecation. There were no urinary symptoms. There was no loss of weight. There was no history of trauma previous to that sustained at the time the patient himself discovered the tumor. He had, however, been riding tractors for a number of years.

Examination.—Examination showed a moderately obese man apparently in good health. Physical examination gave negative results, with the exception of a small tumor in the region of the coccyx. On external palpation, this felt about the size of a hulled walnut, but on bimanual examination with one finger in the rectum it felt about as large as a hen's egg. The coccyx could not be palpated. The mass was firm, movable and slightly tender to pressure. The skin or rectum was not involved.

Operation.—On November 24, under ether anesthesia, a midline incision was made over the tumor. It was found to be ovoid and was covered by a dense capsule. The coccyx was almost completely destroyed by the tumor the upper end of which seemed attached to the lower end of the sacrum. The tumor and the lower end of the sacrum were removed by rather wide dissection. The wound became infected, but by December 21 was entirely healed.

Course.—The patient reentered the hospital on April 12, 1931, complaining of a soreness at the lower end of the spine when sitting or riding in a car. On examination, nothing was palpable in the region from which the tumor had been

removed. He was again seen on June 16, at which time he had no symptoms, and examination again gave negative results.

Pathologic Report.—Dr. Raymond F. Gard made the following report of the tissue removed:

The tumor consisted of an ovoid mass, measuring 7 by 5 by 5 cm. and weighing 104 Gm. It was rather firm and elastic and had a bluish-gray color. The surface was slightly nodular and was covered with a small amount of compressed connective tissue (fig. 1 *A*).

The tissue cut easily, and on section had a grayish-white, moist, cellular appearance similar to fish flesh. Scattered throughout the tissue were numerous irregularly shaped areas of dark brown hemorrhagic-appearing material and a few small areas of bright orange-colored pigment suggesting lipid cell deposits. At one end

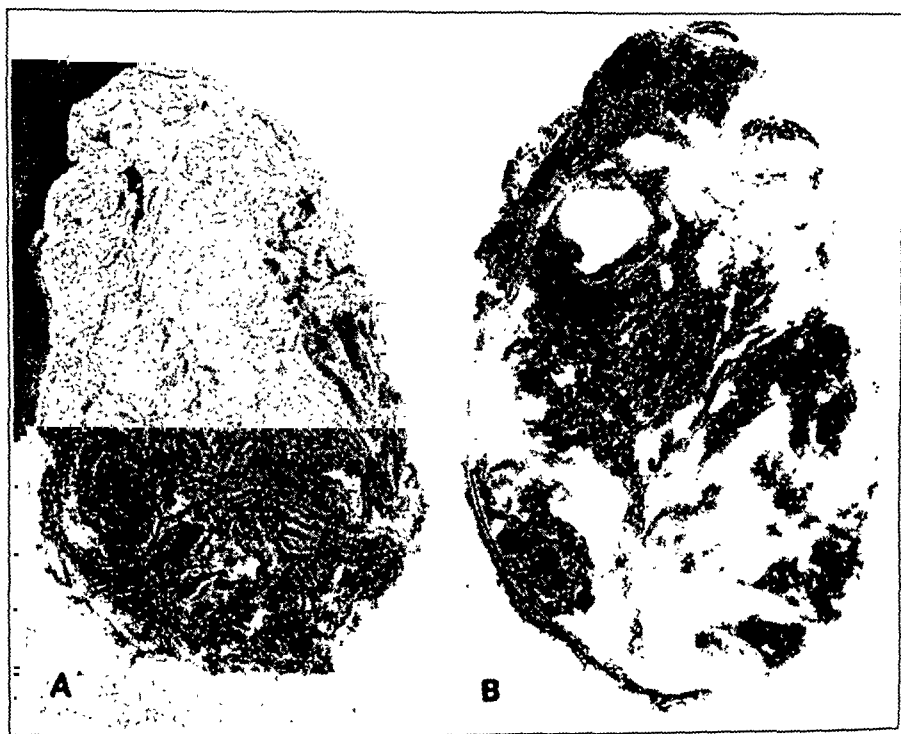


Fig. 1.—*A* is a photograph of the tumor, showing the slightly nodular surface. *B* shows the cut surfaces. The connective tissue capsule is definite. The lighter areas are grayish white, and have the fish flesh appearance. The dark areas consist of hemorrhagic material. At the upper end is a cystic area filled with gelatinous material. Fine white connective tissue trabeculae are seen.

was a cystic space, 1 cm. in diameter, filled with dark gelatinous material. There was only a small amount of stroma, and it was collected into fine trabeculae that traversed the cellular tissue in an irregular manner (fig. 1 *B*).

Histologic section showed the tumor to be divided by irregular strands of fibrous tissue into indefinite areas that varied greatly in size and outline (fig. 2). Some of this stroma showed hyaline change. The cellular tissue enclosed by the fibrous bands was made up of small cells that were uniform in size and staining reaction. They were oval or round and had small, round, densely stained nuclei. Nucleoli were not seen. The cytoplasm was granular, and there was an unusual tendency to vacuolization (*A* in fig. 3). In a few places the vacuoles almost filled the cells,

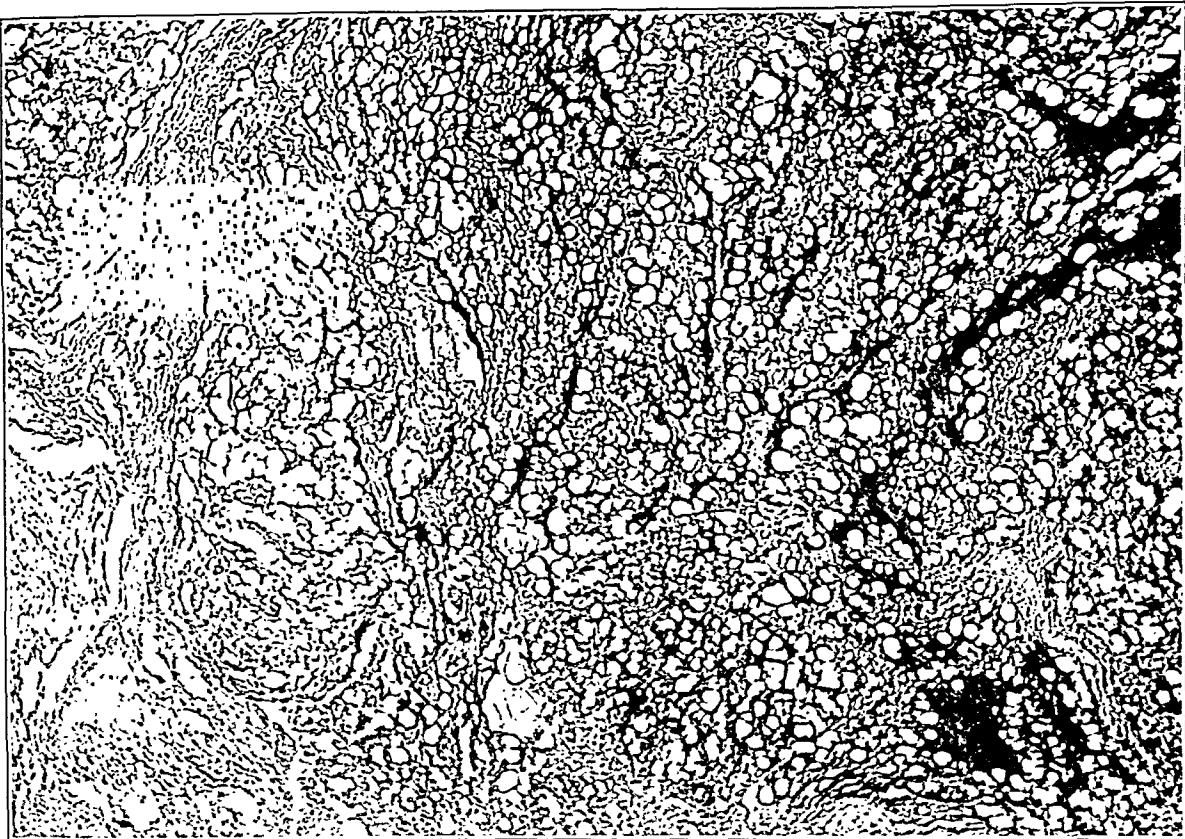


Fig. 2.—The tumor tissue presents the aspect of a highly vacuolated syncytium. Cytoplasmic vacuolization is extreme. Irregular strands of fibrous tissue traverse the section. Dark areas of complete mucoid degeneration are seen; $\times 59$.

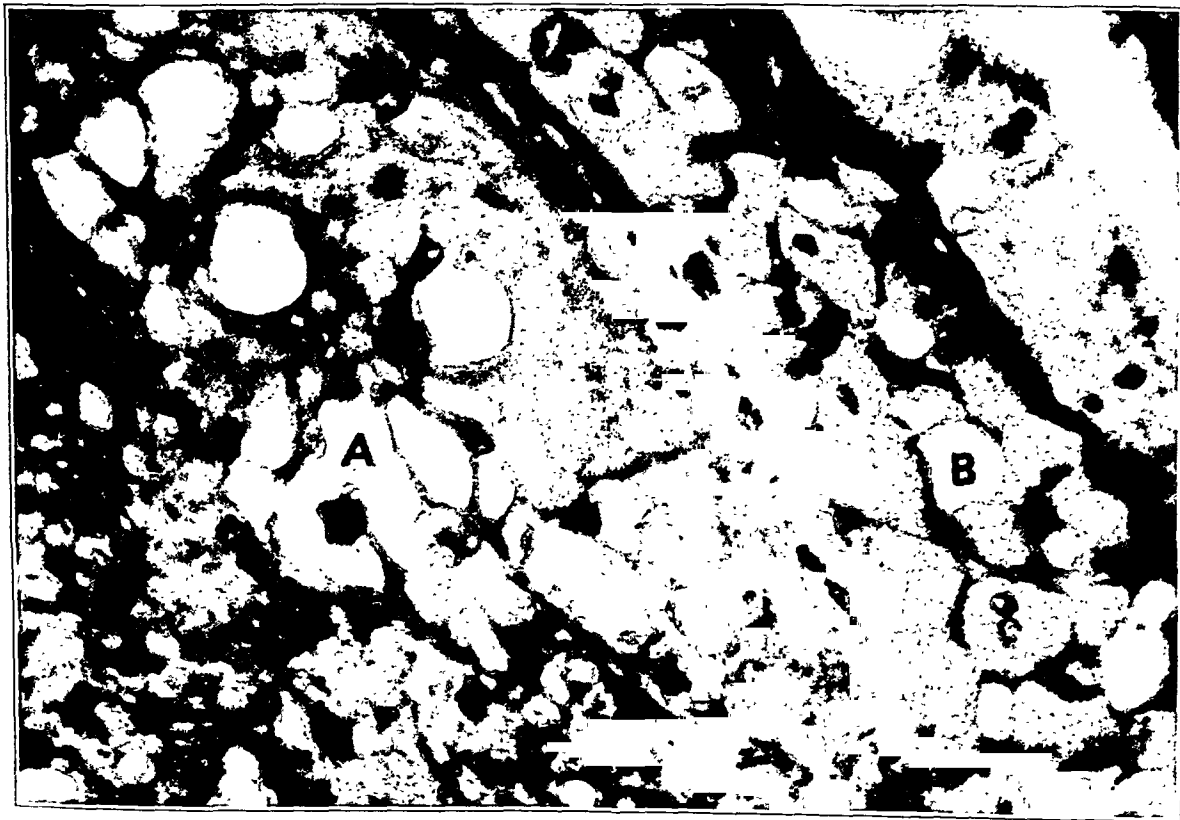


Fig. 3.—The left side of the section (A) shows more, and the right (B) a lesser degree of, degeneration. The area on the left shows complete vacuolization of the cytoplasm with the nuclei occupying the periphery of the cells. The area on the right presents a more solid epithelioid aspect, although beginning vacuolization of the cytoplasm is plainly evident. Several cells contain two nuclei; $\times 450$.

pushing the nuclei to the periphery and forming "signet ring" cells. In many places the cells had undergone complete mucoid degeneration so that the fields showed indefinite, slightly basic, stained, stringy, mucoid material with isolated nests of tumor cells that had not yet degenerated. No mitosis was seen.

There were considerable hemorrhage and some coarsely granular dark brown pigment scattered here and there throughout the sections. Along the fibrous strands there were small collections of lipoid or "foamy" cells (*B* in fig. 3). Blood vessels were scanty.

HISTORY OF CHORDOMA

Luschka,¹ in 1856, described a soft, jelly-like, lobulated tumor at the base of the brain the pedicle of which perforated the dura and base of the skull in the region of the clivus blumenbachii.

Virchow,² in 1857, gave the first good description of these tumors and gave them the name "Ecchondrosis physalifera" because of the vacuolated, degenerated cells surrounded by a bluish hyalin-like substance resembling cartilage.

H. Müller³ first recognized that these tumors were of notochordal origin. He showed that in the spheno-occipital synchondrosis the notochord remains as a soft mass exactly analogous to the nucleus pulposus of the intervertebral disks. He also showed that in the region of the future spheno-occipital synchondrosis the notochord has a tendency to approach the superior surface of the basilar cartilage, and that in the human embryo, along the track of the notochord through the basilar cartilage, a number of little cavities or canals remained filled with notochord-like tissue. He showed that the small tumors described by Luschka attached by their pedicles to similar tissue within the bone, and he also stated at this time that tumors consisting of the same kind of tissue were found on the coccyx.

Henning⁴ reported a sacral tumor in a 7 months fetus, and identified the vacuolated cells with rounded and flattened nuclei that they contained with those of the notochord.

Origin.—The notochord is found at an early stage of the embryo as a rod lying below the medullary or neural groove. It constitutes the basis of the axial skeleton, namely, the spinal column and base of the skull. In the developing embryos of the higher vertebrates it becomes enclosed in the centers of the bodies of the vertebrae and the modified vertebrae forming the base of the skull. Normally, it degenerates early with the exception of a residual collection of cells in the

1. Luschka: Virchows Arch. f. path. Anat. **9**:311, 1856.

2. Virchow: Untersuchungen über die Entwicklung des Schadelgrubes, Berlin, G. Reimer, 1857.

3. Müller, H.: Ztschr. f. rationelle Med. **2**:202, 1858.

4. Henning: Beitr. z. path. Anat. u. z. allg. Path. **38**:593, 1900.

centers of the intervertebral disks known as the nucleus pulposus. Similar aberrant vestiges of notochordal tissue have been demonstrated along the clivus blumenbachii and the sacral and coccygeal regions of fetuses and young infants. These aberrant remnants connect with the notochordal tissue within the bone, and it is from these rather than from the nucleus pulposus that chordomas originate.

The small jelly-like tumors described by Luschka and Virchow never produced symptoms, and Ribbert in 1904 stated that these small collections of notochordal cells were found on the clivus in 2 per cent of his autopsies.

Age of Occurrence.—The youngest patient with chordoma whose case was reported was a child 14 months of age, and the oldest, a man of 79. The majority of chordomas occur after the age of 45, more perhaps in the fifth decade of life. Those within the cranium are discovered earlier, because they begin to cause symptoms when still relatively small.

Sex.—The proportion of males to females affected seems to be about in the ratio of 2:1.

Sites of Occurrence.—Most of the eighty odd cases of chordoma reported have been found on the clivus and in the sacrococcygeal region, the number being about equally divided between these two regions. Three have been reported in the region of the cervical vertebrae, one in the region of the fourth, fifth and sixth dorsal vertebrae and one in the region of the third, fourth and fifth lumbar vertebrae.

The tumors may arise within the spine, anterior or posterior to it. The growth tends to invade contiguous tissues and organs. It may be very extensive, one of the reported cases following connective tissue planes as high as the diaphragm and downward almost to the knee.

Few cases of metastasis of sacrococcygeal chordoma have been reported. In one there were metastases to the lungs, heart, liver, spleen, kidneys, thyroid gland and skin. In two there were liver metastases; in one there was a metastasis over the right scapula, and in another, to the regional lymph nodes. They have been shown to invade veins, but in these particular cases no metastases were found. There has been no reported case of metastasis of the spheno-occipital chordomas, the death of the patient occurring much earlier than from tumors in other locations.

Symptoms.—The earliest and most constant symptom is pain in the sacrococcygeal region. It is not severe at first and may not become so for a long time. It is often described as an ache. The pain occurs earlier in those starting within the bone, while those arising on the posterior surface of the sacrum or coccyx may become very large without producing symptoms. The pain may radiate down the thighs.

As the tumor begins to invade, the rectum, bladder and sacral nerve roots are affected. Obstinate constipation and even intestinal obstruction may occur. Rectal hemorrhage and relaxed anal sphincter with prolapse have been reported.

Difficult urination, incontinence, frequency and pain and burning on urination have been produced.

Motor and sensory paralysis of the extremities, loss of pain, touch and temperature senses over the penis, scrotum, anus and perineum, atrophy of the gluteal and thigh muscles and trophic ulcers of the foot have been reported.

Diagnosis.—The diagnosis is made from the location of the pain and the finding of the tumor. Roentgenograms may be of assistance in some cases. A positive diagnosis, however, can hardly be made without a microscopic examination of the tissue. The most frequent error has been in confusing these tumors with carcinoma of the rectum.

Treatment.—The treatment is wide surgical removal if distant invasion has not taken place. Patients with recurrences should be reoperated on. The tumors are very resistant to the roentgen rays, no benefit seeming to be derived from their use.

Prognosis.—The prospect for complete eradication of the tumor is extremely bad. All of the patients operated on, except those seen in recent years, have died of recurrences. Operation and reoperation when possible prolong the life of the patient. The tumor grows very slowly. The average length of life after operation is six and one-half years. One patient lived nineteen years after the first operation.

SUMMARY

Chordomas develop from aberrant notochordal tissue, chiefly on the base of the sphenoid and in the sacrococcygeal regions.

The sacrococcygeal tumors occur mostly in the fifth decade of life.

They are slowly growing, malignant tumors producing death by extension rather than by metastasis.

They are resistant to the roentgen rays.

They nearly always recur after removal, but life may be prolonged by surgical treatment.

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FORTY-SEVENTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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(Concluded from page 892)

MISCELLANEOUS

Fat Embolism and Trauma.—In an editorial in *The Journal of The American Medical Association*,²⁷ it was stated that while the diagnosis of fat embolism was rarely made, the condition probably occurred with considerable frequency. It gave rise to two distinct clinical pictures. There was a pulmonary type characterized by symptoms of asphyxia before death. Here marked obstruction of the arterioles and capillaries of the lungs was observed. The second type, the cerebral type, showed signs of central nervous system irritation. In this type the fat emboli passed safely through the pulmonary circulation and caused lesions in the brain, heart and kidneys. The greatest incidence of fat embolism was observed in skeletal fractures, although this was probably

27. *Fat Embolism and Trauma*, Editorial, J. A. M. A. **97**:1153 (Oct. 17) 1931.

less than 20 per cent. As much as 40 to 60 cc. of liquid fat was found mixed with blood about the broken ends of bones. Pulmonary fat embolism was more liable to develop when the heart muscle was weak. In the cerebral type of fat embolism three clinical stages were observed, a preliminary stage of from forty-eight to sixty hours before the onset of symptoms, a soporific stage ushered in by dyspnea, restlessness, precordial pain and a high pulse rate, a stage of cerebral symptoms, stupor, coma and death. The cerebral type of fat embolism might be overlooked where there was associated trauma to the head. One important and probably the only true etiologic factor in fat embolism was trauma to the adipose tissue of the body.

Underwater Gymnastics.—Lowman²⁸ summarized for the Council on Physical Therapy the known facts in regard to underwater gymnastics. Many conditions, of which the paralyses following anterior poliomyelitis were probably most important, were amenable to its use. The buoyancy of the water permitted both active and resistive movements, which would be impossible or difficult out of the water. Nervous and mental tension was reduced by the relaxing effect of the warm water. The physical therapist had to have special training before attempting this form of therapy. The commonest error committed was overworking the patient, since fatigue did not become evident as readily under water. Treatments lasting five to ten minutes were often all that patients could tolerate. Chilling the patient was another real danger. Hypochlorite solutions seemed most effective for sterilization of the water. The author stressed the fact that the value of underwater gymnastics was one of physics and not of chemistry.

Tenosynovitis.—Conn²⁹ divided tenosynovitis into three groups: tenosynovitis crepitans, stenosing tenosynovitis and suppurative tenosynovitis. The author was led to believe from clinical observation that rapidity of movements and severe muscular tension were the chief causes of tenosynovitis crepitans and stenosing tenosynovitis. He felt that the endogenic type of suppurative or infectious tenosynovitis was not especially induced by trauma.

According to Montsch and Blau,³⁰ peritendinitis crepitans was common, whereas tendovaginitis stenisans of de Quervain was comparatively rare. One hundred and twenty-one cases were observed in 1930 in an outpatient clinic totaling 16,900 cases (1.39 per cent). It was commonest in the colder months, and apparently followed infections of the upper respiratory tract. Trauma following on focal infection was

28. Lowman, C. L.: *Underwater Gymnastics*, J. A. M. A. **97**:1074 (Oct. 10) 1931.

29. Conn, H. R.: *Ohio State M. J.* **27**:713, 1931.

30. Montsch, P., and Blau, A.: *Deutsche Ztschr. f. Chir.* **231**:550 (July 2) 1931.

the commonest cause. Crepitation, palpable and auscultable, was present together with mild pain and swelling. The lesion persisted as a rule for from two to four weeks. Residues were not uncommon. The lesion was not confined to the tendon and its sheath. Experimentally, the authors showed that while electrical stimulation of the tendo achillis of rabbits for a period of a month caused no reaction, such stimulation in the case of rabbits treated with typhoid vaccine (dead organisms) or streptococci cultures (live organisms) was productive of definite lesions.

Funnel Chest Deformity.—Although some funnel chest deformities were present at birth, Kuhns³¹ believed that most of them developed during the early years of life. Irrespective of any disease background, such as rickets, the deformity was due to a disturbance of respiratory mechanics (particularly a low diaphragm) brought about by generally poor posture. The details of this mechanism were discussed and methods outlined whereby the faulty use of the body might be remedied.

Calcified Deposits in Subdeltoid Bursa.—Mumford³² reported his observations in sixteen cases of calcified deposits in the subdeltoid bursa. He felt that repeated mild trauma with the arm in an abducted position or a single trauma leading to injury of the tendons attached to the greater tuberosity were probably the etiologic factors. The calcareous deposits usually had no relation to the pain. It was not definitely known that the deposit was a calcium salt; it might form and again disappear without apparent cause. Operation for the removal of the deposit in the bursa should never be advised until diathermy has been used. All of the author's patients recovered under diathermy, and the deposits disappeared in almost all cases.

[ED. NOTE.—The evaluation of different methods of treatment for calcified deposits in the subdeltoid bursa is difficult because of the tendency of many of the deposits to undergo absorption spontaneously. Control cases must be used before definite conclusions can be drawn.]

Traumatic Separation of the Symphysis Pubis.—Ekas³³ stated that traumatic separation of the symphysis pubis of any consequence resulted also in injury to the sacro-iliac articulations, and that 8 mm. separation was usually sufficient to produce tearing of the sacro-iliac ligaments. Most patients became symptom-free after rest in bed with support to the pelvic girdle from eighteen to ninety days. Rarely was operation necessary. The author's experience was limited to two cases coming on during late pregnancy.

31. Kuhns, J. G.: *New England J. Med.* **204**:1077 (May 21) 1931.

32. Mumford, E. B., and Martin, F. J.: *Calcified Deposits in Subdeltoid Bursa*, *J. A. M. A.* **97**:690 (Sept. 5) 1931.

33. Ekas, W. L.: *Am. J. Obst. & Gynec.* **21**:680 (May) 1931.

BONE, JOINT AND TENDON SURGERY

Technic of Joint Operations.—Discussing the approaches to joints in general, Payer³⁴ pointed out that the method of approach depended in large measure on the purposes of the operation. Between drainage and arthroplasty were many different sorts of joint operations, for each of which the type of incision might vary. In general, incisions should separate muscle groups, sparing the nerve supply. Osteoplastic removal of important muscle insertions might aid. Rustproof wire was recommended for reposition of bony attachments. Wide periosteal stripping was to be avoided as productive of osteophytes. If capsules were to be cut, those incisions that permitted earliest function were best. Lateral ligaments should be preserved. Only the compartment of the joint to be worked on required opening. Injury to the joint cartilage should be avoided in opening joints, while incisions through extra-articular prominences, as the greater trochanter, were warmly recommended. Skin and deeper incisions should not coincide.

[ED. NOTE.—There is nothing new in Payer's article, but we think that the points of proper anatomic approach, careful asepsis, atraumatic technic and respect and care for exposed tissues cannot be too strongly emphasized, and that it is of interest to find that the German point of view agrees in this respect with ours.]

Tourniquet Paralysis.—Eckhoff³⁵ gave details of fourteen cases of tourniquet paralysis. He enumerated the well known facts that its occurrence in the leg was almost unknown, that the musculospiral nerve suffered more than the median or the ulnar, that the motor fibers were affected more severely than the sensory and that complete recovery was the rule, the sensory fibers recovering in a few days and the motor, on an average, in three months. Eckhoff believed that tourniquet paralysis could be avoided by using an aneroid sphygmomanometer at a pressure of 20 mm. above arterial pressure. Since using this method, he had not had a case of tourniquet paralysis in some hundreds of operations.

[ED. NOTE.—The danger of paralysis resulting is great whenever a tourniquet is used on the upper extremity. We believe that an air pressure cuff may minimize this risk, but that it cannot entirely remove it. For this reason a tourniquet should be used only when absolutely necessary in the case of the upper part of the limb.]

Correction of Madelung's Deformity.—The deformity designated by the name of Madelung was, according to Gazzoni,³⁶ essentially an antero-lateral curvature of the distal third of the radius, but not associated with

34. Payer, E.: *Zentralbl. f. Chir.* 58:976 (April 11) 1931.

35. Eckhoff, Nils L.: *Lancet* 2:343 (Aug. 15) 1931.

36. Gazzoni, M.: *Chin. d. org. di movimento* 16:104 (May) 1931.

an irreducible dislocation of the wrist as frequently described. He believed that it was due to a growth disturbance of the distal radial epiphysis resulting from fracture or disease, and that it was not dependent on abnormal use of the hand. The author advocated oblique osteotomy of the lower end of the radius as a means of correcting both the anterior and lateral deformities, and described a case with bilateral deformity in which this had been done and complete correction obtained.

[ED. NOTE.—Not a small factor in Madelung's deformity is the relative overgrowth of the ulna, and this frequently gives rise to symptoms. Resection of the distal end of the ulna has been advocated, and some of the editors have found this a satisfactory method.]

Injuries of the Knee Joint.—Dunn³⁷ reported 522 cases of injury of the knee joint. Half of these were lesions of the semilunar cartilages (in proportion of two and a half internal to one external). In more than a quarter of the cases the lesion was indefinite and defied accurate diagnosis.

Operation was performed 139 times on the internal semilunar and 46 times on the external semilunar cartilage. The lesions of the internal semilunar cartilage found at operation were: detachment or fracture in the anterior half, 19; fracture of the posterior half, 64; bucket handle, 35; no definite lesion, 21. Those of the external semilunar cartilage were: fracture in the anterior half, 11; fracture in the posterior half, 21; bucket handle, 4; cystic degeneration, 3, and no definite injury, 7.

When a satisfactory lesion of the cartilage was revealed at operation, it was Dunn's practice to remove as much of the cartilage as possible, leaving the posterior third. In only three cases in his experience had this remnant become loose subsequently and necessitated a second operation for its removal. When from the history Dunn was convinced that a semilunar cartilage had been damaged, and he found at operation that the internal semilunar was normal, he proceeded immediately to explore the external cartilage. Occasionally both cartilages were damaged. In the series were thirty-four cases of injuries to the internal lateral ligament, in no case was the rupture complete, and operation was never required. Complete tear of the internal lateral ligament never occurred with an injury to a semilunar cartilage. On the other hand, of the seven cases of injury to the external lateral ligament four were complete ruptures, necessitating operation. On seven occasions, Dunn had had to operate a second time to remove a neuroma of the patellar branch of the internal saphenous nerve, which had been divided at the first operation. Dunn now made his skin incision parallel to this cutaneous nerve and retracted it before opening the capsule of the joint.

37. Dunn, Naughton: Brit. M. J. 2:639 (Oct. 10) 1931.

Dunn's experience of the operation performed for the repair of a ruptured crucial ligament was that the operation for the first six months appeared a perfect success, but that after that time anteroposterior movement returned and necessitated the permanent wearing of a brace.

Lantzounis³⁸ made a study of all the patients at the New York Orthopedic Hospital between January, 1920, and August, 1928, on whom operation had been performed for a derangement of a semilunar cartilage. Results were obtained in 139 patients who had undergone 144 operations. The results were 85 per cent excellent and 15 per cent good. There were no postoperative infections of the knee joint. A hypermobile meniscus not necessarily split or detached was recognized as a clinical entity. The amount of trauma did not necessarily determine the degree of injury to the cartilage. The ratio of injury of the internal to the external cartilage was 8:1. A longitudinal incision was used in the great majority of cases.

[ED. NOTE.—Both of the foregoing articles are valuable, especially from the statistical standpoint. Hypermobility without injury is recognized by both authors as a cause of symptoms. Of interest is the difference in the ratio between injuries of the internal and external semilunar cartilages. The same variation has likewise been reported in many previous articles. It probably depends on differences in the interpretation of the pathologic changes.]

Reconstruction of the Patella.—A method of reconstructing the patella was described by Pirrone.³⁹ The patient, a man of 50, had a destructive lesion of the patella (primary tuberculosis), for which the entire patella was resected. After this wound had healed, a patella was reconstructed by removing a round total cortical thickness graft from the upper third of the right tibia. The graft was sutured to the quadriceps and patellar tendons, with the cortex toward the joint. After twenty days, immobilization was discontinued. The published roentgenograms and photographs showed excellent reconstruction of the patella and an active range of motion in the knee of about 100 degrees.

[ED. NOTE.—Though perhaps desirable, it is not essential to function to replace a resected patella. One of the editors has observed a case in which the patella was resected for osteomyelitis in which there is now excellent motion with freedom from pain and in which the patella has not reformed or been replaced.]

A New Operative Procedure for the Correction of Calcaneal Deformity.—In an effort to find a physiologic method for limiting the motion of the tibio-astragalar joint by operative means without inter-

38. Lantzounis, L. A.: Surg., Gynec. & Obst. **53**:182 (Aug.) 1931.

39. Pirrone, A.: Chir. d. org. di movimento **16**:3 (July 14) 1931.

fering with the articular cartilage in calcaneal deformity, Putti⁴⁰ developed the following procedure after noting that an arthritic patient had obtained a limited motion in his tibio-astragalar joint by the proliferation of the anterior margin of the superior astragalar joint surface. The operation was performed as follows: Through an anterior median incision opening the ankle joint, the body of the astragalus was exposed. With a 20 mm. osteotome, a cut was made into the body of the astragalus in the horizontal plane from before backward, just below the anterior margin of the superior articular surface. Then, by gradually widening the anterior portion of the osteotomy to about 1.5 cm., the calcaneal deformity was overcome. A fragment of bone taken from the astragalar neck was driven into this space to maintain the correction. The foot was then held in maximum plantar flexion in plaster for two months. Five patients have been operated on successfully by this method; in one case the results were reported ten months after operation. The article was illustrated by diagrams and roentgenograms which showed excellent correction of the calcaneal deformity.

[ED. NOTE.—The operation described by Putti, consisting essentially of a horizontal transverse osteotomy of the body of the astragalus with separation of the anterior portions of the fragments by a free bone graft serving as wedge, seems simple, and is deserving of consideration as a means of correcting calcaneal deformity.]

FRACTURES

Local Anesthesia in the Reduction of Fractures.—Carothers⁴¹ reported the use of local anesthesia in the reduction of fractures in 270 patients. Ten to 20 cc. of a 2 per cent solution of procaine hydrochloride was injected into the hematoma about the fracture. The author listed as advantages the cooperation of the patient, the ability to reduce the fracture without skilled assistance and the opportunity for further attempts at reduction after roentgen examination without additional anesthesia, since the original injection was effective for one and one-half hours. In only two of the cases was it necessary to resort to general anesthesia. No infections which could be attributed to the anesthetic occurred.

Physiology of Bone Repair.—Murray⁴² believed that the four essential factors for securing healing of a fracture were: (1) death of the tissue; (2) adequate growth of the granulation tissue; (3) a local concentration of calcium to act as a calcium source, and (4) proper p_H of

40. Putti, V.: Chir. d. org. di movimento **16:1** (May) 1931.

41. Carothers, R. G.: Local Anesthesia in Reduction of Fractures, J. A. M. A. **97:517** (Aug. 22) 1931.

42. Murray, C. R.: Ann. Surg. **93:961** (May) 1931.

tissue fluids in the particular region involved. He felt that the blood calcium and phosphorus had little or nothing to do with the healing of fractures. He did not believe that bone repair came from a specific bone-forming cell, the osteoblast, and stated that approximately 60 per cent of the tissue that subsequently became calcified was derived from tissue outside the bone, and that the portions of the bone that helped in repair were the soft tissue elements originating from the periosteum, endosteum and areolar tissue about the blood vessels in the bone canals. He felt that the reason why delayed union or nonunion resulted so frequently in fractures of the femoral neck and the lower half of the tibia was the lack of blood supply, the absence of muscular tissue surrounding these sites, and in the case of the femoral neck, the presence of synovial fluid which in itself delayed growth.

To obtain optimum conditions for healing, he would provide (1) early and accurate replacements of fragments, (2) rapid restoration of normal lymph and vascular circulation, (3) meticulous care of compound wounds and (4) open operation and reduction when the conditions justified and when careful operative technic was available.

The origin of the calcium appearing in hematomas had been investigated by Fuss and Faber.⁴³ They produced subcutaneous and intramuscular hematomas in dogs and compared the calcium content of the hematoma with that of the blood stream. With allowance for the concentration of the solids in the hematoma, its calcium content was found to be considerably elevated in the living animal after three to eleven days. Presumably the calcium was brought via the blood stream. The author suggested that hematomas about fractures acted as calcium depots from which the growing callus could obtain calcium according to its requirement, in a form ready for use.

A number of workers have described the favorable action of injected bone and callus extracts in the promotion of bone growth. Specific active bone-autolysates might offer new fields for therapy in the healing of bone. Hoffmeister and Terchmann⁴⁴ described the use of an albumin-free extract of callus as a skin test. It was injected intracutaneously, and on the basis of a hundred patients observed, the authors stated the test was apparently quite specific when active bone-healing was in progress. A positive reaction might be obtained, though of less intensity, by the use of blood serum of a patient with a healing fracture. The injection of callus extract locally into a delayed union of seventeen weeks' duration was followed by consolidation in eighteen days. The specific substance in the blood stream that permitted the eliciting of a positive

43. Fuss, H., and Faber, K.: *Deutsche Ztschr. f. Chir.* **232**:658 (Aug. 24) 1931.

44. Hoffmeister, W., and Terchmann, T.: *Deutsche Ztschr. f. Chir.* **231**:380 (May 7) 1931.

skin reaction was present in a pair of twins with bone cysts and in a patient with tuberculosis of the bone as well.

[ED. NOTE.—Opinions in respect to the exact mechanism of bone repair are still inconclusive, as indicated by the contradictory evidence of these three articles. Murray, as a result of careful studies, is convinced that bone repair is a physicochemical process controlled by local factors at the seat of fracture. Fuss and Faber's findings point to the blood stream as the source of the calcium, while Hoffmeister and Terchmann's experiments, as yet incompletely checked, would point to the presence of some specific substance elaborated during the process of bone repair.]

Plaster Yoke Dressing for Fractures of the Clavicle.—The use of a plaster yoke, a figure of 8 plaster dressing including both shoulders for fracture of the clavicle, was reported by Billington.⁴⁵ The plaster was applied with the patient recumbent or sitting and with the injured shoulder lifted upward and backward. The author cited as advantages that the dressing supported the weight of the shoulder securely, and that immediate use of the arm was possible.

[ED. NOTE.—A similar type of dressing as that described has been employed at the Massachusetts General Hospital for several years with satisfaction.]

Skeletal Extension for Fractures of the Humerus.—Baumann⁴⁶ recommended highly the use of skeletal extension by Kirschner's wire for the treatment of fractures of the lower end of the humerus. The wire was inserted under local anesthesia, either in the olecranon or in the lower end of the humerus, and was connected to a weight and pulley fixed to an overhead frame in such a way as to secure vertical traction on the arm. The forearm was supported on an anterior plaster splint, the distal part of which was likewise suspended from the overhead frame and counterpoised so that the elbow remained at a right angle. Reposition was accomplished automatically. If necessary, a padded roll could be applied to the upper part of the arm by means of which a lateral pull could be exerted if there was deviation of the shaft of the humerus. A certain amount of motion of all the joints was possible from the first, and the treatment was painless as well as efficient. The wire should be removed in approximately three weeks. Consolidation occurred early, and in the author's opinion was stimulated by the early motion. He employed the method regularly in children.

[ED. NOTE.—The same method was previously advocated by Zeno for fractures of the lower end of the humerus, implicating the elbow.

45. Billington, R. W.: South. M. J. 24:667, 1931.

46. Baumann, Ernst: Beitr. z. klin. Chir. 152:260 (April 29) 1931.

Baumann's report is to be regarded as confirmatory evidence that the method is effective and safe.]

Isolated Fractures of the Pisiform Bone.—Divnogorski⁴⁷ reported a case of fracture of the pisiform bone, and found previously published reports of four other cases in a review of the literature. He attributed the injury to the action of the flexor carpus ulnaris and abductor minimi digiti muscles during a fall. In four of the five collected cases healing occurred uneventfully after treatment by immobilization. In the fifth case extirpation was performed after three months because of persistent disability of the hand, but relief was not obtained after abduction, and extravasation of blood about the hypothenar eminence was the outstanding finding on examination. The diagnosis depended on roentgen examination, and views made from different angles might be required.

Kümmell's Disease.—Although admitting that the condition was rare, Rigler⁴⁸ reported a case that he felt justified in calling Kümmell's disease. The patient, a woman aged 55, fell downstairs, and the vertebrae that later showed the changes known as Kümmell's disease were two months after injury roentgenologically normal, and were considerably removed from the original site of injury. It was to be noted that the changes in the bone were quite similar to those so well discussed by Schmorl and attributed to an injury of the intervertebral disk, causing a rupture with expansion of the nucleus pulposus and secondary atrophy of the vertebral body.

Results of Fractures of the Neck of the Femur.—Stern, Reich, Heyman and Papurt⁴⁹ investigated the end-results in seventy-nine cases of intracapsular fractures of the neck of the femur, in all but five of which reduction was done in the Whitman position of abduction and internal rotation with application of a plaster spica. The usual plan of treatment was to leave the plaster on for three months, and follow this with a Bradford abduction splint or a Thomas walking splint. Briefly, the results of union were as follows: up to 39 years, of nine patients all obtained union; from 40 to 50 years of age, of ten patients only 30 per cent obtained union; from 51 to 60 years of age, 87 per cent obtained union; from 61 to 70 years of age, 78.5 per cent obtained union.

Reporting briefly their experience with one hundred and ninety patients with fracture of the neck of the femur, Wustmann and Albreck⁵⁰ concluded that initial accurate replacement of the fractured

47. Divnogorski, B. F.: *Deutsche Ztschr. f. Chir.* **232**:648 (Aug. 24) 1931.

48. Rigler, L. G.: *Am. J. Roentgenol.* **25**:749 (June) 1931.

49. Stern, W. G.; Reich, R. R.; Heyman, C. H., and Papurt, L. E.: *Surg., Gynec. & Obst.* **53**:250 (Aug.) 1931.

50. Wustmann and Albreck, H.: *Deutsche Ztschr. f. Chir.* **231**:516 (June 3) 1931.

surfaces was the most essential feature of treatment. Medial fractures of the neck were best treated in the abduction-internal rotation position by plaster cast fixation. Lateral fractures of the neck close to or involving the trochanters did well with constant traction to the leg and the hip in the position of abduction and internal rotation. Old people did better in plaster fixation than might be imagined, the danger of pneumonia and thrombosis being less than one might expect. Of sixty-eight patients with lateral fractures of the neck treated in traction, nineteen (28 per cent) died of embolism, pneumonia or cardiac disease; of twenty-nine with medial fractures of the neck treated in plaster, 27 per cent died.

[ED. NOTE.—The figures published by Stern and his co-workers indicate that beyond the age of 39 the chances of getting bony union depend less on the exact decade in which the patient belongs according to age than on local factors at the seat of fracture and the apposition obtained by the reduction. The figures published by Wustmann and Albreck show that the death rate conforms pretty closely to the experience reported previously in this country, and is about the same regardless of whether the patient is treated in plaster or by traction.]

Fractures of the Anterior Superior Portion of the Os Calcis Due to Indirect Violence.—Dachtler⁵¹ called attention to fractures of the anterior superior portion of the os calcis. He had observed twenty-six such injuries since 1928, and therefore considered it not a rare occurrence. All but two were industrial accidents, and were produced by a truck being pushed forward on the posterior aspect of the ankle joint, forcibly flexing the ankle. All patients were treated in plaster; and weight-bearing was not permitted for four weeks. Then a molded plate was applied, which was worn for an additional month, during which time the patient was bearing weight with the aid of crutches.

[ED. NOTE.—The fractures referred to appear to have been sprain fractures with small spicules of bone, and in our opinion such injuries are better treated by adhesive strapping and active use, rather than by plaster fixation.]

DISLOCATIONS

Retrosternal Dislocation of the Clavicle.—Discussing retrosternal dislocation of the clavicle, Niessen⁵² stated that the lesion was of infrequent occurrence, and that when reduction was not obtained by conservative methods such as the application of a clavicular T splint or other devices tending to pull the shoulder backward, open operation was invariably indicated. The necessity of reduction arose from the danger

51. Dachtler, H. W.: Am. J. Roentgenol. **25**:629 (May) 1931.

52. Niessen, Hubert: Deutsche Ztschr. f. Chir. **231**:405 (May 7) 1931.

to the retroclavicular structures, trachea, esophagus, pleura, vessels and nerves. An unusual motion of the shoulders might cause the loose end of the clavicle to rupture or otherwise injure them.

The author recommended the passage of a rolled fascia lata band through double holes drilled in the clavicle and sternum. A similar operation had been urged for anterior dislocation at this site. He did not consider a plastic operation on the origins of the sternocleidomastoid and pectoralis major muscles, as suggested by Meyer for the anterior dislocation, necessary. He had operated on two patients with retrosternal dislocation of the clavicle with success.

Dental Treatment of Habitual Dislocation of the Lower Jaw.—Reichenbach⁵³ reported that in a period of six months he had treated four patients with habitual luxation of the lower jaw. Each had an associated prognathism. The condition was caused by capsular relaxation. The author urged the use of retentive dental appliances (elastic bands, tooth-affixed hinges or pressure plates). Operation should be advised only after attempts had been made to obtain capsular shrinkage by the aforementioned conservative means.

AMPUTATIONS

Experiences with the Krukenberg Kineplastic Amputation.—Reviewing the published experiences of other surgeons and combining his own observations with theirs, Krukenberg⁵⁴ stated that the general impression of the results obtained by his kineplastic amputation of the forearm, which created muscularly controlled pincers, was much in favor of the procedure. He listed nine surgeons whose experience with the operation had been satisfactory, and presented several striking results of his own. In certain cases remarkable strength had developed in gripping, and as a rule the radial-ulnar grip was more powerful than a normal thumb-forefinger grip. Fine motions were likewise possible, although these suffered most. There had been a few modifications in the technic of the operation since it was first described in 1917. Kümmell had slightly modified the skin incision and transplanted three quarters of the extensor digitorum communis and flexor digitorum communis tendons to the radius instead of but half, as in Krukenberg's technic, since the radius was to become the movable portion of the forearm. The Putti osteotomy was decried as liable to interfere with future adduction of the "blades."

The operation might be done in clean cases, as Porzelt had urged, at the primary amputation, and it had also been done, although with less resultant power (atrophied muscles), as late as nine years after amputa-

53. Reichenbach, E.: *Deutsche Ztschr. f. Chir.* 231:470 (June 3) 1931.

54. Krukenberg, H.: *Arch. f. klin. Chir.* 164:191 (May 15) 1931.

tion. Krukenberg related a single failure, and that occurred in a blind patient. Mobilization was started from ten to twenty days after operation, pronation and supination being particularly stressed. Prostheses were possible, but not necessary or valuable. Before he performed the operation, the matter was put up to the patient for decision, since the cosmetic aspect of the resulting situation was of considerable importance.

[ED. NOTE.—We feel that in the United States the unsightly appearance of the forearm stump after Krukenberg's operation would more than counterbalance the functional gain resulting from the ability to grip except in the case of bilateral amputations of the arm. Krukenberg's advice to submit the matter to the patient for decision should be followed to the letter.]

RESEARCH

Further Observations on Transplantation of Epiphyseal Cartilage Plates.—Repeating the experiments, the results of which he reported in 1915, Haas⁵⁵ again attempted to cause regeneration of the epiphysis after transplantation of the growth disk. His results were decidedly disappointing and not in agreement with those of Hellen (1915) and Fohl (1929). The following group of experiments were performed: (1) reimplantation of the epiphyseal cartilage plate with a very thin layer of osseous tissue; (2) reimplantation of the reversed epiphyseal cartilage plate; (3) reimplantation of the entire epiphysis and epiphyseal plate; (4) reimplantation of the epiphysis with varying lengths of the diaphysis and (5) reimplantation of the epiphyseal plate with a portion of the epiphysis and diaphysis. In twenty-seven such experiments growth after transplantation of the epiphyseal cartilage plate resulted in only two instances, and in these it was noted that the plate had not been completely excised at the time of the operation.

Metabolism of Skeletal Muscle Undergoing Atrophy.—Hines and his co-workers⁵⁶ studied the metabolism of skeletal muscle undergoing atrophy of denervation in dogs in comparison with the metabolism of the skeletal muscle in the opposite normal limb. Studies were made of the sugar, lactic acid, oxygen and carbon dioxide content of the blood entering and leaving the limb. The findings were similar in the normal and denervated limb. This suggested to the authors that an intact nerve supply was not necessary for normal metabolism of skeletal muscle.

Virulence of Staphylococcic Medullary Bone Infections.—Rollo⁵⁷ experimentally introduced saline suspensions of staphylococcic cultures

55. Haas, S. L.: Surg., Gynec. & Obst. **52**:958 (May) 1931.

56. Hines, H. M.; Lese, C. E., and Knowlton, G. C.: Am. J. Physiol. **98**:50, 1931.

57. Rollo, Salvatore: *Pediatrics* **39**:949 (Sept. 1) 1931.

into the medullary bone cavities of young rabbits and dogs. He found that the virulence of the infection was much greater following the intramedullary inoculation of organism than by the intravenous, intraperitoneal or subcutaneous routes. Furthermore, if organisms were cultured on a marrow medium, subsequent medullary inoculations were followed by still more virulent infections. The author felt that the medullary cavity of the bones provided an especially good culture medium for staphylococci.

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